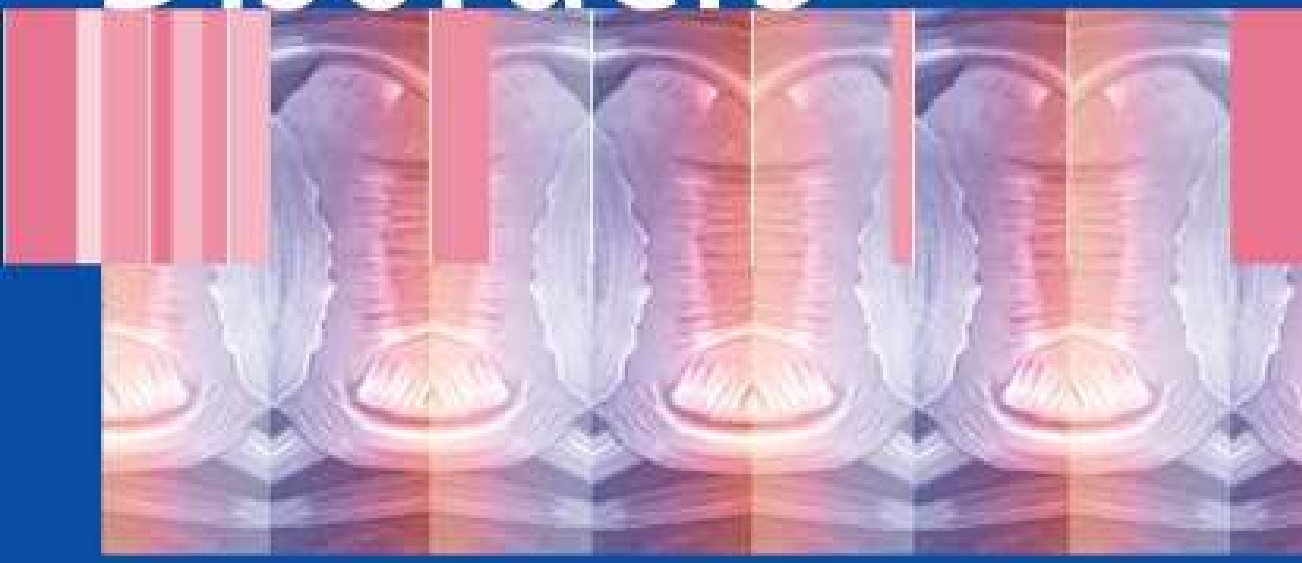
Jane W. Chan

Optic Nerve Disorders



Diagnosis and Management

Springer

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Jane W. Chan, MD

Associate Professor of Ophthalmology and Neurology, University of Kentucky College of Medicine, Lexington, Kentucky, USA

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This book is dedicated to my parents, Tom and Rosalie Chan—especially to my mother for her unconditional love and support. I also appreciate my mentors, Drs. William F. Hoyt, John L. Keltner, and David P. Richman, who have given me guidance in my career.

Preface

This book presents the salient features of optic nerve disorders, encompassing optic neuritis, papilledema, ischemic optic neuropathies, compressive and infiltrative optic neuropathies, traumatic optic neuropathies, nutritional and toxic optic neuropathies, hereditary optic neuropathies, and optic disc tumors. Chapters 1 to 9 outline key clinical aspects of each of these disorders. Chapter 10 illustrates some newer applications of optical coherence tomography (OCT) in monitoring optic nerve-related processes causing retinal nerve fiber layer loss and in ruling out retinal disorders. Chapter 11 discusses the adjunctive role of visual evoked potential (VEP), multifocal VEP, electroretinogram (ERG), and multifocal ERG in the diagnosis of more challenging visual problems, especially in distinguishing them from macular disorders and psychogenic etiologies.

Although there are excellent textbooks covering various aspects of neuro-ophthalmology, this book is intended for any physician, including ophthalmologists, neurologists, and neurosurgeons. Fellows, residents, and medical students can acquire an up-to-date knowledge base to better help their patients with optic nerve disorders. It is a unique reference that combines the applications of some newer diagnostic techniques with the symptoms and signs approach to visual loss in a useful and practical format.

Jane W. Chan, MD

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Optic Neuritis

Jane W. Chan

Introduction

Although neurologists usually diagnose and treat multiple sclerosis, the visual loss that often accompanies this disease often presents to an ophthalmologist or neuro-ophthalmologist for evaluation. It is an inflammation of one or both optic nerves resulting in (usually) temporary visual loss. It affects young to middle-aged adults between 16 and 55 years of age. The female-to-male ratio is 2:1. Children often are affected bilaterally, whereas adults are affected unilaterally. The annual incidence of acute optic neuritis has been estimated in population-based studies to be between 1 and 5 per 100,000.[1,2] Clinically definite multiple sclerosis (CDMS) is apparent at the onset of optic neuritis in 15% to 20% of patients with optic neuritis; another 40% will later experience a multiple sclerosis attack.[3] The clinical diagnosis and advances of understanding the pathogenesis and current recommended treatment of this disorder are outlined here.

Clinical Presentation of Optic Neuritis

Symptoms

The loss of central vision is the major symptom reported in more than 90% of patients who have acute optic neuritis. Others who have normal visual acuity may complain of loss of peripheral vision to one side in the superior or inferior fields. The patient usually experiences mild orbital pain above or behind the eye, but the pain is mild even with severe visual loss. This dull retrobulbar pain may precede or occur concurrently with the visual loss. It also may be aggravated by upward eye movement and may occasionally last for as long as several weeks.[4] The optic nerve inflammation may stimulate the trigeminal innervation of the optic nerve sheath to cause this orbital pain. As visual acuity decreases over the next several days, the pain usually subsides when visual loss is maximal. Loss of color vision or dullness in the vision is also more commonly noticed by patients than photophobia. Other less common symptoms are perception of phosphenes (flashing lights with noise or eye movement) and decreased depth perception.[5]

Signs

Visual Acuity

Visual acuity worsens over several hours, days, or even minutes and ranges in severity from 20/20 to no light perception. The degree of visual loss does not correlate with the final visual outcome. Visual loss usually peaks at several days to a week. Maximal improvement in visual function typically occurs within 2 to 3 weeks and at most within 6 months or more.[4]

Visual Field

Patients who have acute optic neuritis can present with a wide variety of visual field

defects, most commonly a central scotoma. Less frequent defects may include an arcuate scotoma, a superior or inferior altitudinal scotoma, peripheral constriction, a cecocentral scotoma, and bitemporal or a left or right hemianopic defect. In the Optic Neuritis Treatment Trial (ONTT), this wide variety of baseline patterns of visual field loss had limited usefulness in differentiating optic neuritis from other optic nerve disorders.[6] During the recovery phase, the central scotoma reduces to a small, dim, central or paracentral defect. Occasionally, an arcuate scotoma may persist. Less severe optic neuritis may cause only "blurry vision" and a relative scotoma that eventually resolves. Because of the Uhthoff phenomenon, as is discussed later, patients whose optic neuritis have resolved can have large variations in visual field results on different days and at different times on the same day.[7]

Contrast Sensitivity and Color Vision

Contrast sensitivity and color vision are both reduced in acute optic neuritis. The loss of contrast sensitivity is often proportionate to or sometimes worse than the loss of visual acuity.[4] The color dysfunction is also usually more severe than the visual acuity level.[8] Although Ishihara color plates are most commonly used in the clinic, the Farnsworth–Munsell 100-hue test has been shown to be more sensitive and specific.[9] The shortened version with caps 22 to 42 has a similar sensitivity for serial monitoring of dyschromatopsia after optic neuritis. The dyschromatopsia is related to the time course of the disease. More blue-yellow defects occur in the acute stage of optic neuritis, whereas more red-green defects occur after 6 months.[10] In the ONTT, no particular type of color vision defect was consistently associated with optic neuritis. The type of defect appeared to be inconsistent in individual patients as they recovered. The kind of color defect did seem to correlate with spatial vision at the time of testing, but the type of color defect at 6 months did not correlate with the severity of initial visual loss.[11] Patients also have decreased sensation of brightness in the affected eye.[10]

Pupillary Abnormality

The relative afferent pupillary defect is almost always present in anterior (swollen disc) or retrobulbar neuritis. If it is not present, then one should seriously consider other ophthalmic problems, such as a coexisting optic neuropathy in the fellow eye or other causes of visual loss unrelated to an optic neuropathy. Subclinical optic neuritis in the fellow eye is not uncommon. In the Optic Neuritis Study Group, 48% of patients who had unilateral optic neuritis and no prior optic neuritis in the fellow eye had an abnormal visual field in the asymptomatic eye. Approximately 68% of the asymptomatic fellow eyes had baseline visual field defects that mostly affected the peripheral rim or were diffuse; 62% of these visual field defects were classified as minimal. Most patients recovered normal visual field with varying pattern and location of sensitivity loss. Between 10% and 20% of these patients believed that their vision was normal, despite having abnormal visual acuity, color vision, or contrast sensitivity.[6] These clinical abnormalities are consistent with the pathological evidence of demyelination and atrophy found in the optic nerves of patients who have subclinical optic neuritis.[12,13]

Fundus Findings

Fundus findings also help to localize the site of the optic nerve lesion. Lesions that are adjacent to the optic nerve head cause papillitis (anterior optic neuritis) with minimal blood vessel enlargement and rarely peripapillary hemorrhages (Figure 1.1).[14] Vitritis is present in anterior optic neuritis caused by infections or inflammations (sarcoidosis, syphilis, tuberculosis, Lyme disease) and may be associated with multiple sclerosis (MS) as part of an intermediate uveitis. More posterior lesions (retrobulbar optic neuritis) do not produce papillitis.[12] Unilateral retrobulbar optic neuritis and papillitis both are part of the multiple sclerosis spectrum of presentation.[5] In retrobulbar optic neuritis, the optic disc is normal. Irrespective of the location of the lesion, 75% of patients who have MS, including those who have had a previous subclinical attack, eventually develop diffuse or

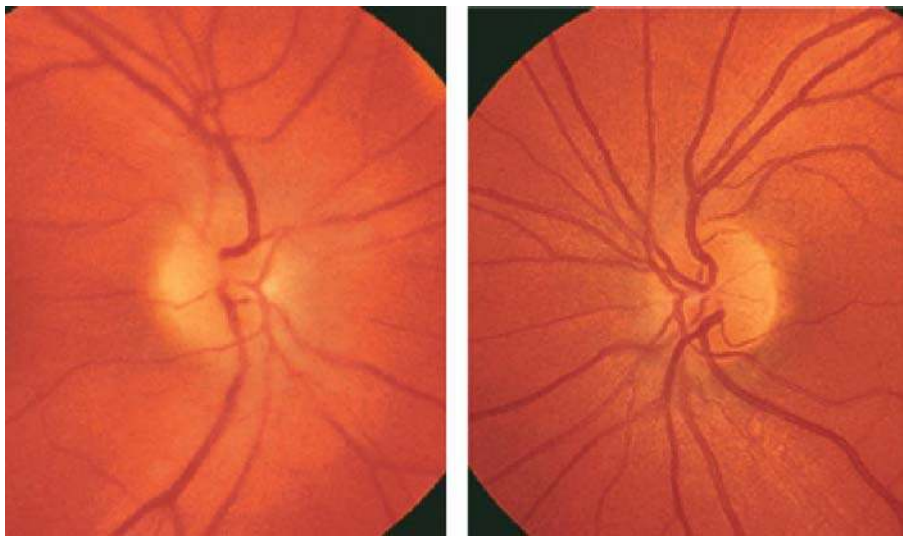

FIGURE 1.1. The left optic disc (*right*) is normal, but the right optic disc (*left*) is mildly swollen, as seen in anterior optic neuritis. (Reprinted from Spalton et al.,[14] with permission from Elsevier.)

temporal optic disc pallor and nerve fiber layer atrophy.[5] The optic disc swelling and the disc pallor both are nonspecific findings in optic neuritis. Peripheral retinal venous sheathing may also be seen in MS, but this finding is not specific for MS as it may also be found in sarcoidosis, pars planitis, intermediate uveitis, lymphoma, and other localized ocular conditions. This sheathing represents the visible clinical sign of perivascular lymphocytic infiltration and edema of MS lesions. The vascular inflammation occurs in a region that lacks myelin and oligodendrocytes, suggesting that the vascular endothelium may be the initial site for the formation of new lesions. The presence of peripheral retinal venous sheathing has been shown to be correlated with the development of MS.[15]

Differential Diagnosis of Optic Neuritis

The acute monocular visual loss suggestive of optic neuritis should alert the ophthalmologist and neurologist to consider vascular optic nerve disorders.[16] Acute ischemic optic neuropathy (AION) is an infarction of the prelaminar anterior optic nerve as a result of an occlusion of the two main posterior ciliary arteries that supply the optic nerve and choroid. The orbital pain of MS-related optic neuritis, when it is severe and when it occurs or worsens during eye movement, is often a useful feature in differentiating acute optic neuritis from anterior ischemic optic neuropathy.[17] A course that is painless and does not progress to significantly improved visual function (at least two lines of visual acuity improvement) after several weeks does not suggest optic neuritis.[4] Furthermore, altitudinal rather than generalized disc swelling, disc pallor, arterial attenuation, and peripapillary hemorrhages are features much more commonly seen in AION than in optic neuritis.[18] AION is much more common in patients who are older than 50 years and who have symptoms of giant cell arteritis and an elevated sedimentation rate.[5] It may also occur independently of giant cell arteritis.

Another neuro-ophthalmic disorder to consider in the differential diagnosis of optic neuritis is Leber's hereditary optic neuropathy (LHON). Males between 15 and 35 years of age are more commonly affected than females. Impairment of ganglion cell function results in visual loss that typically begins painlessly and

centrally in one eye followed by the second eye over days or months. Circumpapillary telangiectatic microangiopathy, swelling of the nerve fiber layer around the disc (pseudoedema), and absence of leakage from the disc or papillary region on fluorescein angiography are the key features distinguishing LHON from other causes of optic disc edema.[19] Genetic testing for the mitochondrial DNA mutations 11778, 3460, and 14484 can also help confirm the diagnosis of LHON.[20]

Other systemic infections, granulomatous inflammations, and autoimmune diseases besides MS may present with optic disc edema as part of a neuroretinitis, posterior uveitis, or posterior scleritis. Parainfectious optic neuritis usually develops 1 to 3 weeks after the onset of a viral or bacterial infection.[21] It is more common in children than in adults and may be unilateral, but it is more often bilateral. It is usually caused by demyelination associated with swollen optic discs. It may occur with no evidence of neurological dysfunction or with a meningitis, meningoencephalitis, or encephalomyelitis. Cerebrospinal fluid is usually abnormal when neurological manifestations are present. Visual recovery after parainfectious optic neuritis is often excellent. Postviral optic neuritis may be caused by underlying adenovirus,[22] coxsackievirus,[23] hepatitis A[24] and B,[25] cytomegalovirus,[26] Epstein–Barr virus (EBV),[27] human immunodeficiency virus type 1 (HIV-1),[28] measles,[29] mumps,[30] rubella,[31] varicella zoster,[32,33] and herpes zoster.[34] Optic neuritis may also be seen in bacterial infections including anthrax,[35] beta-hemolytic streptococcal infections,[36] brucellosis,[37] cat scratch disease,[38] meningococcal infection,[39] pertussis,[40] tuberculosis,[41] typhoid fever,[42] and Whipple's disease.[43] Postvaccination optic neuritis is more often anterior and bilateral. It may develop after vaccination with Bacillus Calmette–Guerin (BCG),[44] hepatitis B,[45] rabies virus,[46,47] tetanus toxoid,[48] variola virus,[49] and influenza virus.[50] However, in a recent matched case-control study of 1131 patients in the U.S. military with optic neuritis, no statistically significant associations between optic neuritis and anthrax, smallpox, hepatitis B, or influenza vaccines were observed between 1998 and 2003.[51]

In sarcoidosis, the optic neuritis may be anterior or retrobulbar; it can be the presenting feature or may occur during the course of the disease.[52] In contrast to demyelinating optic neuritis, in sarcoidosis the optic disc may have a lumpy, white appearance that suggests a granulomatous reaction and may be associated with vitritis. Unlike the course of recovery in primary demyelinating optic neuritis, which is not steroid dependent, vision may decrease again in sarcoid once steroids are tapered or stopped. This steroid-dependent course of recovery is atypical for demyelinating optic neuritis and suggests an infiltrative or nondemyelinating inflammatory process, such as sarcoidosis.[52]

Both anterior and retrobulbar optic neuritis may occur in HIV-infected patients with cryptococcal meningitis,[53] cytomegalovirus (CMV) infection,[54,55] herpesvirus infection,[56] syphilis,[57] tuberculous meningitis,[58] and various fungal infections.[59] HIV is capable of invading the optic nerve itself. Opportunistic infections usually occur with a low CD 4 count. CMV papillitis is necrotizing, and CMV inclusion bodies have been isolated in the optic nerve.[60] Herpes zoster papillitis can precede outer retinal necrosis.[61] Retrobulbar optic neuritis from herpes zoster can either precede or follow acute retinal necrosis, based upon a study of six patients with central nervous system (CNS) imaging abnormalities associated with retrobulbar optic neuritis that were temporally related to acute retinal necrosis.[62] Optic neuritis related to *Cryptococcus* and toxoplasmosis usually presents concurrently with CNS infection.[63]

Optic neuritis can be seen in patients with West Nile virus. It appears to be self-limited, and vision improves with or without corticosteroids over the course of several months. Diagnosis is based upon abnormal serum West Nile virus titers.[64] Rarely, patients with toxoplasmosis may also develop optic neuritis.[65] Optic neuritis in patients with autoimmunodeficiency syndrome (AIDS) may also represent infection of the optic nerve by HIV itself.[66,67]

Regarding spirochetal infections, both anterior and retrobulbar optic neuritis may be seen in patients with Lyme disease.[68]

In severe acute sphenoid sinusitis, the infection may spread posteriorly to the optic nerve in the orbital apex or within the optic canal, causing retrobulbar optic neuritis and acute visual loss.[69]

In neuroretinitis, intraocular inflammation itself may cause optic disc edema. Unlike the visual loss from damage to the optic nerve in demyelinating optic neuritis, the visual acuity is limited by the degree of vitreous inflammation or by secondary changes in the macula, such as cystoid macular edema, associated with optic disc edema after cataract extraction. Swelling of the peripapillary retina may be observed in patients with anterior optic neuritis. Lipid exudates in a star configuration may also develop in the macula of the affected eye. Neuroretinitis may be seen in infections involving *Borrelia burgdorferi* (cat scratch disease),[70] toxoplasmosis,[71] hepatitis B,[72] and influenza.[73] Syphilis can cause both neuroretinitis and optic perineuritis, which are seen more frequently as part of syphilitic meningitis[74] Coxsackievirus infection may also cause an optic neuritis or neuroretinitis.[75]

In posterior uveitis, optic disc edema and profound visual loss may occur with inflammation of the retina and choroid. Posterior uveitis may be associated with some form of systemic disease. The bacterial infections include *Treponema pallidum*,[76] *Borrelia burgdorferi*,[77] *Leptospira interrogans*,[78] *Brucella*,[79] *Nocardia asteroides*,[80] *Mycobacterium tuberculosis*,[81] and *Neisseria meningitides*.[82] Viruses causing posterior uveitis include cytomegalovirus,[83] herpes simplex,[84] herpes zoster,[85] rubella,[86,87] rubeola,[88] and HIV.[89] Parasites, such as *Toxoplasma*,[90] *Toxocara canis*,[91] and *Onchocerca volvulus*,[92] and fungi, such as *Candida*,[93] *Histoplasma capsulatum*,[94] *Cryptococcus neoformans*,[95] *Aspergillus*,[96] *Coccidioides immitis*,[97] and *Blastomyces dermatitides*,[98] may also cause optic disc edema in the clinical setting of posterior uveitis.

In the setting of autoimmune-related posterior uveitis, vasculitis of the optic nerve in Wegener's granulomatosis may cause optic disc edema.[99,100] Papillitis occurs in the acute phase of the posterior uveitis in at least 25% of cases of Behcet's disease and is related to microvasculitis of the arterioles feeding the optic nerve.[101] Retinopathy more often than choroidopathy is seen in systemic lupus erythematosus; the optic neuritis may occur with or without posterior uveitis.[102] Hyperemia of the optic disc and optic neuritis, in addition to uveitis, choroiditis, and exudative retinal detachments, can be seen in Vogt–Koyanagi–Harada disease.[103]

Various malignancies may also invade the uvea and optic nerve. Up to 18% of acute leukemias and 16% of chronic leukemias have some leukemic infiltration of the optic nerve, causing optic disc edema and hemorrhage.[104] Intraocular lymphoma, malignant melanoma, and metastatic lesions may also spread to the optic nerve.[105–107]

Regarding posterior uveitis in primary ocular disorders, severe disc edema and cystoid macular edema can be commonly seen in birdshot retinochoroiditis.[108] Papillitis occasionally may be present in acute posterior multifocal placoid pigment epitheliopathy (APMPPE)[109] and multiple evanescent white dot syndrome (MEWDS).[110] The optic nerve is usually not affected in serpiginous choroiditis, but optic neuritis has been reported so far in one patient with recurrent disease.[111]

Optic disc edema may be seen in about 20% of patients with posterior scleritis, which usually presents with unilateral periocular pain and decreased vision with little or no redness. Patients more than 50 years of age usually have an associated systemic disease and are more likely to experience visual loss, mostly from macular changes or optic atrophy related to the posterior scleritis. The more common associated systemic diseases are rheumatoid arthritis, Wegener's granulomatosis, systemic vasculitis, relapsing polychondritis, and other autoimmune diseases similar to those seen in anterior scleritis, and, rarely, systemic lymphoma and multiple myeloma.[112]

Less commonly, optic neuritis may be the only initial manifestation of an underlying autoimmune disease not associated with MS. Young females present with unilateral or bilateral decreased vision and usually do not have overt signs or symptoms of a preexisting collagen-vascular disease, such as systemic lupus erythematosus. Laboratory tests for antinuclear

antibody (ANA) and double-stranded DNA are most useful in confirming the diagnosis of lupus.[113] Patients who have occult symptoms of rheumatic disease or who have positive family histories for collagen-vascular diseases may initially present with optic neuritis and/or transverse myelitis. The diagnosis of antiphospholipid antibody syndrome in these patients is confirmed by the presence of elevated serum immunoglobulin M (IgM) anticardiolipin antibody.[114] Another form of optic-spinal MS more commonly seen in Asians is associated with significantly high levels of antithyroid autoantibodies. It is thought that this MS variant could represent a pathogenetic link between antithyroid autoimmunity and a subgroup of optic-spinal MS in Japanese that is not related to human T-cell lymphotropic virus (HTLV)-1 disease.[115]

Rarely, optic nerve inflammation can be part of a paraneoplastic syndrome. Optic neuritis has been documented in cases involving bronchial carcinoma, oat cell carcinoma, and lymphoma. Pathological data have shown that inflammation and demyelination, not the carcinomatous or lymphomatous invasion of the optic nerve, cause the decreased vision (see following section on paraneoplastic optic neuropathies).[116–119]

Pathogenesis of Optic Neuritis

Demyelination

Fifty percent of MS patients have clinical evidence of having had optic neuritis (at autopsy, almost 100% have optic neuritis), and 20% of them have it as their presenting sign.[120] The initial event before demyelination is the breakdown of the blood-brain barrier through the inflammation of the vascular endothelium. With the lack of oligodendrocytes in the retina, perivenular retinal sheathing represents this vascular inflammation without demyelination. The venous sheathing occurs as a clinically silent retinal disease before the development of optic neuritis. This feature may not be visible on funduscopic examination but may be demonstrable on fluorescein angiography.[121] The basic defect in optic neuritis/MS involves demyelination of the optic nerve, which blocks or slows the conduction of axonal transmission or decreases the amplitude of the nerve action potential. Various degrees of visual loss result from this process. The perivenular demyelinating plaques from optic nerves of patients who have acute MS reveal similar pathology to the periventricular plaques found elsewhere in the brain. These plaques show a perivascular cuffing of T and B cells, edema in the myelin nerve sheaths, and subsequent myelin breakdown. In optic neuritis the axons of the optic nerve are usually spared, resulting in good clinical recovery. More advanced lesions elsewhere in the CNS white matter often involve axonal degeneration, resulting in physical or mental disability. On histopathology, macrophages engulf the degraded myelin products and glial cells proliferate to cause permanent conduction block with no clinical recovery.[122,123]

Cell-Mediated Damage

The neuroimmunological factors that mediate demyelination of the optic nerve involve cell-mediated cytotoxicity. In one study, 76% of the patients who had optic neuritis were found to have encephalitogenic, myelin basic protein (MBP), cerebroside, and ganglioside antibodies.[124] Patients who had optic neuritis/MS and patients who had isolated optic neuritis and cerebrospinal fluid (CSF) oligoclonal bands both had encephalitogenic antibodies. Elevated T-cell-mediated cytotoxicity against the encephalitogenic peptide is a highly specific marker for demyelination in MS. Optic neuritis patients who test positive for this antigen have a greater risk of developing clinically definite MS.[125] The increased CSF MBP- and MBP-reactive B cells in patients who had optic neuritis could correlate with the process of early myelin breakdown or restoration.[126] Although magnetic resonance imaging (MRI) generally has been accepted as the marker of disease activity in patients who have MS, the concentration of MBP in CSF also has been useful as a marker during acute exacerbations of MS. It is significantly correlated with the visual acuity in patients who have optic neuritis, the Kurtzke

expanded disability status scale score in patients who have MS, the cerebrospinal leukocyte count, intrathecal immunoglobulin G synthesis, and the cerebrospinal albumin concentration quotient.[126] Furthermore, the activated T cells recognizing these MBP peptides secreted interferon-gamma (IFN-γ).[127] The cytokine profile of IFN-γ, interleukin-4, and tumor growth factor-β in patients who had optic neuritis was the same as that found in patients who had CDMS.[127] The production of these cytokines is much greater in the CSF than systemically, which underscores the autonomy of the immune responses in the CSF. The upregulation of these cytokines has been demonstrated in very early MS, as manifested by acute optic neuritis associated with more than two MS lesions on MRI of the brain and oligoclonal IgG bands in CSF.[127] The activated IFN-γ-producing T cells in the inflammatory foci of optic nerve sections in rats with acute experimental allergic encephalomyelitis showed elevated levels of calpain expression.[128] Calpain has been shown to degrade axonal and myelin proteins, including MBP, neurofilament proteins, and myelin-associated glycoprotein, and may, therefore, play a role in the pathogenesis of optic neuritis in MS.[129] Furthermore, the proinflammatory cytokines tumor necrosis factor and lymphotoxin in the CSF were found to be elevated in patients who had optic neuritis to the same degree as patients who had CDMS.[130]

Anti-MBP and antimyelin phospholipid protein (PLP) antibodies may significantly contribute to the pathophysiology of optic nerve damage.[131] Patients who had isolated optic neuritis were found to have significantly more anti-PLP-secreting B cells in the blood than patients who had other neurological diseases; anti-PLP antibody is more specific for demyelinating disease than is anti-MBP antibody.[132] It is also associated with the subtype of MS that has less frequent inflammation in the CSF and CNS parenchyma, whereas anti-MBP antibody is associated with the more common form of MS, which has more frequent prominent inflammatory CSF and CNS features.[133] The increased CNS synthesis of both anti-MBP and anti-PLP antibodies is found in patients who have optic neuritis, whether idiopathic or MS related. The synthesis of these antibodies is also not associated with the presence of the human leukocyte antigen (HLA)-DRB1*1501 gene.[134]

Genetic Factors

Based on studies in Canada[135] and Finland,[136] first-degree relatives have a 25 to 50 times greater risk of being affected than the general population. Overall, the risk is highest in monozygotic twins, with a concordance rate of about 30% in dizygotic twins and in other siblings less than 10%, providing strong evidence for genetic factors in MS.[137–140] In siblings, the earliest symptoms of the disease tend to cluster by age rather than by year, suggesting that genetic factors influence the onset of the disease.[141–143]

Based on association studies using the case-control design testing specific candidate genes and studying sporadic and familial cases, the only consistently replicated finding has been an association with the HLA-DR2 allele within the major histocompatibility complex (MHC) on chromosome 6. Data from the study by Haines et al. in 1998[143] strongly indicate that sporadic and familial MS share a common genetic susceptibility. These data also support the hypothesis that a genetically determined immune response plays a primary role in the pathogenesis of MS. Furthermore, the MHC locus probably represents less than half of the entire genetic etiology of MS. Families not segregating the HLA-DR2 allele appear to have no linkage to the MHC and therefore must be influenced by other genes.[143]

Based on the study by The Multiple Sclerosis Genetics Group in 2002,[144] the association of DR2 in families with diverse clinical presentations suggests there exists a common genetic basis to various clinical phenotypes of MS. The MHC genes appear to primarily influence penetrance, whereas other loci modulate specific phenotypes, such as location in the brain or spinal cord, demyelination, and severity of inflammation.[145] Epigenetic factors, such as the selection of different disease-inducing antigens, also influence the location and severity of experimental allergic encephalitis phenotypes induced with different encephalitogenic

peptides.[146] It is likely that a similar interplay of genetic and epigenetic factors operate in human MS. The HLA region at 6p21[147] and several other suggestive loci have been proposed.[148] Therefore, non-HLA genes or other epigenetic factors must modulate disease expression. Locus heterogeneity at the HLA region suggests a distinct immunopathogenesis in DR2 negative patients.[149] Different classes of HLA may have different roles in susceptibility to MS. The DR2, A23, and B21 allele is associated with the evolution of optic neuritis to CDMS. The high prevalence of A23 and DR2 alleles in CDMS patients compared with the normal population may suggest an important role for these alleles in the development of MS. The B51 allele may be a protective factor against the development of optic neuritis in the normal population.[150]

Mitochondrial DNA mutations may also contribute to the cause of MS. Pathogenic mitochondrial DNA point mutations usually are not associated with typical optic neuritis/MS. Only certain secondary LHON mutations have been associated with MS and optic neuritis.[149] This partial overlap between the two diseases may be related to the association of MS with a mitochondrial DNA haplotype (a set of mitochondrial DNA polymorphisms) within which LHON mutations preferentially occur.[149]

Epidemiological Factors

Age, sex, and race all play some role as risk factors for the development of MS. The onset of optic neuritis at a young age is a predictive factor in the development of MS. One study[151] found that the relative risk for MS increases by a factor of 1.7 for each decade less than 54 years of age in adults. There is also a tendency for females to develop MS after optic neuritis, such that 69% of 47 females and 33% of 20 males developed MS after approximately 15 years since their initial attack of optic neuritis. Based on the 2-year data from the ONTT, Caucasians were found to be at higher risk than African Americans to develop MS, even after 4 years of follow-up.[152,153]

The place of residence in relationship to the distance from the equator during the first 15 years of life is a major risk factor for the development of MS after optic neuritis. People who are younger than 15 years will acquire the risk of the country to which they migrate. It is still not certain whether people who migrate later in adulthood retain the risk of their original country or the risk of their new residence.[154]

The fall and winter months also are risk factors. One study[155] showed that 43% of 42 patients developed MS with an onset of optic neuritis between October and March; only 29% of 44 patients whose onset of optic neuritis occurred between April and September developed MS.

Diagnostic and Prognostic Tests

Typical Optic Neuritis

According to the conclusions of the ONTT, MRI of the brain is a good predictor of MS and should be considered to assess the risk of future neurological events of MS and for treatment decision making. Forty percent to 70% of patients who have isolated optic neuritis have been reported to have periventricular white matter signal abnormalities on T_2-weighted MRI scans (Figure 1.2). In the ONTT, the 2-year risk for developing CDMS was 3% if the patient initially had a normal brain MRI scan and 36% if the patient initially had two or more lesions within the central white matter. The 4-year risk for having CDMS was 13% if the MRI scan of the brain initially was normal, 35% if the MRI scan showed one to two abnormalities, and 50% if the MRI scan showed three or more abnormalities in the white matter.[152,153] According to the Optic Neuritis Study Group, the 5-year cumulative probability of developing CDMS after optic neuritis was 30% for all treatment groups. Neurological impairment was slight. At 5 years, 16% of 202 patients who had no brain MRI lesions developed CDMS, whereas 51% of 89 patients who had three or more MRI lesions did. Presence of previous nonspecific symptoms also was predictive of CDMS. Low-risk factors for CDMS included optic disc swelling, lack of pain, and mild visual acuity loss.[156] The number of MRI lesions highly

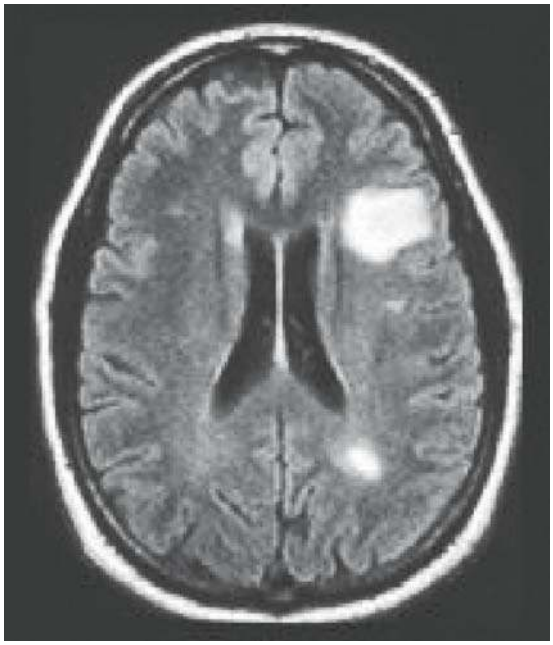

FIGURE 1.2. Most MS activity in the CNS is clinically silent. This proton density-weighted image demonstrates multiple T_2-hyperintense lesions in both hemispheres. In the setting of acute optic neuritis, the multiple white matter lesions in a number and pattern atypical for patient age are considered supportive of the diagnosis of multiple sclerosis.

correlated with the 5-year risk for CDMS, but a normal brain MRI scan did not preclude the development of CDMS.[156] After 10 years of follow-up in the ONTT,[157] patients with optic neuritis with greater than or equal to one brain MS lesion had a 56% chance of developing CDMS. Those with no brain MS lesions had a 22% chance of developing CDMS. Factors that conferred a low risk of developing CDMS among patients with optic neuritis without lesions on brain MRI included the following: male gender and the atypical features of optic neuritis, such as no light perception, absence of pain, optic disc edema, peripapillary hemorrhages, and retinal exudates. In a recent study by Brex et al.[158] of patients who first presented with optic neuritis or other isolated syndromes clinically suggestive of MS, CDMS developed in 88% of patients with abnormal MRI findings at presentation and in 19% with normal initial MRI results. After the 8-year follow-up of 26 patients who had acute monosymptomatic optic neuritis, 54% of them developed CDMS. Furthermore, patients who presented with optic neuritis actually developed much milder MS.[159] Overall, it is believed that most patients who have a history of optic neuritis and who are destined to develop MS do so within 7 years of the onset of visual symptoms.[1,159]

The signs of optic nerve inflammation may be visualized on neuroimaging. In some cases of typical optic neuritis, diffuse enlargement of the optic nerve can be seen on fat-suppressed MRI scans with and without contrast enhancement on coronal orbital sections.[160] Gadolinium enhancement and T_2-signal abnormalities correlated with ultrastructural studies showing inflammatory infiltrate and expansion of the extracellular space.[161] Demyelinative lesions seemed to progress from the optic nerve insertion at the globe to the orbital apex.[162] MRI can also detect foci of enhancement along the nerve, which represent demyelinative lesions. It is important to note that similar MRI enhancements along the optic nerve can also be seen in patients who have ischemic, infectious, or radiation-induced optic neuropathies, but they are not pathognomonic for a demyelinative process.[162]

Based on the ONTT, ancillary laboratory testing in patients who have typical optic neuritis does not yield any clinically useful information: these results included routine blood tests, ANA, fluorescein treponemal antibodies (FTA-ABS), chest X-ray, and CSF analysis (as detailed later). Based on the experience of the ONTT, it was concluded that CSF analysis was not necessary in the routine evaluation of patients who present with a typical profile of acute optic neuritis. Most CSF tests added little additional information to MRI results for predicting the 2-year development of CDMS.[163] However, a more recent study showed some predictive value in the assessment of CSF of patients who have MS: those who had both abnormal MRI and elevated intrathecal IgG synthesis had a 46% increased risk for developing MS after 4 years, compared with 33% if they had only an abnormal MRI.[164]

Furthermore, a positive ANA did not have any effect on the patient's course or response to any treatment given.[4] Therefore, besides neuroimaging, no further laboratory testing is required for typical optic neuritis.

The visual evoked potential (VEP), a measure of afferent visual function, is not useful when optic neuritis is suspected. The poor visual acuity during acute disease precludes adequate measurement of the P100 latency. On the other hand, the VEP is useful later in determining whether the episode of visual loss involved demyelination.[165,166] Recently, the multifocal VEP latency delay has been shown to help in predicting progression to future MS. In a study of 22 patients with optic neuritis, 36.4% with prolonged latencies on multifocal VEP progressed to CDMS compared with 0% of those with normal latencies.[167]

Optical coherence tomography (OCT) is a noninvasive procedure that can accurately and reproducibly measure the thickness of the peripapillary retinal nerve fiber layer (RNFL). It is now being used in clinical investigations to assess axonal preservation and degree of neuroprotection.[168]

Atypical Optic Neuritis

MRI of the orbits with fat suppression is indicated for patients who have the following characteristics of atypical optic neuritis: (1) older than 45 years, (2) bilateral presentation, (3) a vertical hemianopic visual field defect, (4) progression of the optic neuritis for more than 2 weeks, and (5) recent sinusitis. It is imperative to rule out compressive lesions, such as aneurysms and tumors in the intraorbital, intracanalicular, and intracranial areas.[152] Serological and CSF studies should be performed on any patient who presents signs or symptoms and course of disease that are unlike typical optic neuritis and who are suspected of having an underlying systemic or local infection or inflammation. Laboratory tests should include erythrocyte sedimentation rate (ESR) and ANA for connective tissue disease, rapid plasma reagin and FTA-ABS for syphilis, and serum angiotensin-converting enzyme for sarcoidosis.

In the ONTT, CSF analysis did not detect any additional, unsuspected diagnoses other than MS. A normal initial CSF after optic neuritis did not exclude development of MS in the future. Certain serological and CSF findings in isolated optic neuritis are associated with MS: (1) MS CSF oligoclonal bands, (2) CSF anti-MBP antibody, (3) CSF anti-PLP antibody, and (4) a cytokine profile of activated T cells (interferon-γ, interleukin-4, and tumor growth factor-β) similar to that found in patients who have CDMS. These CSF and serological factors all were detected in patients who had isolated optic neuritis and who eventually developed CDMS.[124,127,169] Based on the Optic Neuritis Study Group assessment, the presence of CSF oligoclonal bands was useful as a predictive factor for developing MS 5 years after optic neuritis only when the brain MRI scan was normal.[170] It is generally accepted that an abnormal MRI scan at the time of optic neuritis is significantly related to later MS development. Further studies on the exact role of oligoclonal bands in the development of MS after optic neuritis are in progress.[163]

Visual Prognosis

Young to middle-aged adults, predominately females, who present with optic neuritis as the initial manifestation of MS have a better prognosis of nondisabling MS than those who present initially with other MS features.[169] After 1 year of follow-up in the ONTT, 69% of patients had visual acuity of 20/20 or better, 93% had 20/40 or better, and 3% had 20/200. These results were similar in each treatment group.[171]

Other factors besides age may also affect visual prognosis. Longer lesions of the optic nerve and involvement of the intracanalicular segment are related to slightly less complete visual recovery.[172] The presence of Uthohff's phenomenon, transient visual blurring associated with an elevation of body temperature following optic neuritis, is most common in patients with other evidence of MS.[173–176] Scholl et al.[176] reported that these patients were more likely to have an abnormal MRI of the brain and that

they were more likely to develop MS. Uthohff's symptom was present in about 10% of patients in the ONTT 6 months after the onset of optic neuritis. It is important to note that Uhtohff's phenomenon may also occur in healthy patients after optic neuritis, in patients with Leber's optic neuropathy,[177] and in patients with optic neuropathies from other causes.[178] Uthohff's symptom results from a reversible conduction block in impulse transmission by demyelinated nerve fibers.[179]

Visual Residual Deficits

Optic Disc Pallor and Relative Afferent Pupillary Defect

Specific residual eye signs serve as indicators of previous optic nerve damage. Despite good recovery of vision, the afferent pupillary defect does not always persist after resolution of unilateral acute optic neuritis. It serves as a marker for earlier optic nerve dysfunction. The optic disc pallor, located diffusely or temporally, persists irrespective of the degree of visual recovery. Retinal nerve fiber layer defects also can be seen.[180]

Color Vision Defect

One of the most common residual visual deficits in patients whose optic neuritis resolved was defective color vision as tested with the Farnsworth–Munsell 100-hue color test.[181] Despite the return of visual acuity to 20/20 or better, 32% of cases had residual visual field defects after 6 months using a Humphrey Field Analyzer.[172] Patients often continue to complain of visual difficulties months after their attack of acute optic neuritis. In the ONTT, 215 patients perceived their vision to be worse than it was before their optic neuritis, even though 66% had normal visual acuity, 30% had normal contrast sensitivity, 55% had normal color vision, and 58% had no significant visual field defects.[181] These patients may have subtle visual fields defects not detected by conventional perimetry. They complain of disappearing "holes" in their field of vision and the reappearance of the "fill-ins" for these holes while more new holes form. This "Swiss cheese" visual field phenomenon also occurs in other causes of optic nerve disease.[181]

Contrast Sensitivity Abnormality

No matter how good the Snellen visual acuity recovery, contrast sensitivity usually remains abnormal in resolved cases of optic neuritis and in subclinical cases.[182] Brightness sensitivity is also reduced in most patients whose unilateral optic neuritis has resolved.[181]

Visual Evoked Potential Abnormality

The VEP usually reveals a prolonged latency after the resolution of acute optic neuritis. This indication of impaired optic nerve conduction persists even after visual acuity returns to 20/20. Only the amplitude of the VEP may be normal.[183,184]

Other Risk Factors for the Development of Multiple Sclerosis

Recurrent Optic Neuritis

Some features of optic neuritis can increase the risk of developing subsequent MS. Many studies suggest that nonspecific symptoms associated with the initial attack and previous optic neuritis are risk factors for later MS.[185] Recurrent optic neuritis increases the incidence of MS,[186] but bilateral optic neuritis in adults has not been confirmed as a risk factor.[187] The probability that visual acuity will return to normal decreases with each recurrence.[188] The visual acuity after recovery from optic neuritis does not influence the later development of MS.[188]

Optic Neuritis in Children

Pediatric optic neuritis usually presents bilaterally associated with headache. Periorbital pain that worsens with eye movements supports a diagnosis of optic neuritis. It is not often related

to MS, but is often associated with a postinfectious or postimmunization etiology. It is often preceded by a febrile prodromal illness, such as a bacterial or viral infection.

Optic neuritis in children usually presents with visual loss, relative afferent papillary defect, abnormal optic disc appearance, visual field defects, and color vision abnormalities. Papillitis is seen in 60% to 70% of children and in only 35% of adults.[189] Both clinical and VEP parameters improve until vision recovers. In a recent 1-year follow-up study of 12 children with optic neuritis (6 with bilateral and 6 with unilateral optic neuritis),[190] 14% of all eyes had residual visual loss and 85% had abnormal optic disc appearance; relative afferent pupillary defects (67% at onset), visual field defects (58.5% at onset), and color vision defects (56% at onset) resolved 1 year later. VEP were abnormal in 83% of eyes initially and in 56% at the end of 1 year. Complete clinical and VEP recovery occurred in 3 children. Visual recovery in the other children was attained within 1 year.

Children who present unilaterally have a greater tendency to develop MS.[191–193] The incidence of MS following unilateral and bilateral childhood optic neuritis has ranged from 5.2% to 55.5% in different studies.[193–195] Kriss et al.[192] found that MS developed in 3 of 29 (10.3%) children with bilateral optic neuritis and 3 of 10 (30%) children with unilateral optic neuritis over a mean follow-up of 4.6 years. Although children with bilateral optic neuritis have a lower incidence of MS than those with unilateral optic neuritis, the risk in those with bilateral optic neuritis is not negligible.[192] In 8 of the 30 patients from the Kennedy and Carroll series[195] that developed MS over a mean follow up of 8 years, 4 had simultaneous bilateral disc swelling. According to Riikonen,[193] MS developed in 7 of 8 (87.5%) patients with unilateral optic neuritis and in only 2 of 15 (15.4%) patients with bilateral optic neuritis over a mean follow-up of 7 years. This study showed that all patients who later developed MS had a second attack of optic neuritis within 1 year of the first attack. Morales et al.[196] found that children who developed MS were, on average, older at presentation with optic neuritis than those who did not develop MS (Table 1.1).[197]

Table 1.1. A comparison of features of optic neuritis in adults and children[197]

Adult optic neuritis	Pediatric optic neuritis
Unilateral	Bilateral
Usually associated with pain upon eye movements	Usually associated with headache
Retrobulbar optic neuritis	Papillitis
Usually idiopathic	Usually postinfectious or postimmunization
Likely to recur as CNS inflammatory relapses and to progress to MS	NOT likely to have demyelinating relapses or progress to MS

Treatment of Optic Neuritis

Corticosteroids

Visual recovery is accelerated with the use of intravenous (IV) methylprednisolone within the first 2 to 3 weeks of onset of visual symptoms. In the ONTT, visual acuity improved to 20/25 after only 4 days of IV methylprednisolone, compared with 15 days of no therapy or oral steroids. After 1 month, the recovery rate was similar in treated and placebo-oral steroid groups. Most visual recovery is completed by 1 month. Some further improvement may occur 6 months to 1 year later.[198]

The major conclusions of the ONTT related to treatment consist of guidelines in the use of corticosteroids. Treatment with high-dose IV methylprednisolone followed by 2 weeks of oral prednisone accelerated visual recovery but did not give any long-term benefit to ultimate visual outcome. At 6 months, the IV corticosteroid group had better contrast sensitivity and visual color function. One year later, all the groups had similar recovery of the foregoing functions.[199] Conversely, treatment with oral prednisone alone did not improve the ultimate visual outcome. In fact, it increased the risk of a new attack of optic neuritis in either eye. Within the first 2 years of follow-up in the ONTT, a new attack of optic neuritis occurred in 30% of the oral prednisone group, 16% of the placebo group, and 13% of the IV methylprednisolone group.[199]

Treatment with IV methylprednisolone followed by 14 days of oral prednisone decreased the 2-year rate of development of MS, especially in patients who had magnetic resonance signal abnormalities. Fewer patients developed neurological signs and symptoms of MS during that period, and fewer of them met criteria for CDMS.[200] Of the 150 patients who were treated with corticosteroids and who had two or more lesions on MRI scans, 36% developed CDMS within 2 years, whereas only 5% of 202 patients who had normal or minimal abnormalities on MRI scans did so. The patients in the ONTT had a brain MRI scan within 9 days of the onset of visual loss. The side effects of corticosteroid therapy as used in the ONTT were minimal.[198,201]

Despite some criticisms about the ONTT, it is considered a hallmark for a well-controlled prospective clinical trial on the evaluation and treatment of optic neuritis.[201] Table 1.2 summarizes the treatment recommendations of the ONTT. The treatment outcome was not related to the effect of steroids and more likely reflected the natural history of MS. In contrast to the immunomodulatory agents that delay the progression of MS, steroids promote more rapid recovery from the demyelinating attack. It has been shown that patients with abnormal brain MRI results at presentation are more likely to progress to CDMS within 2 years of onset than those who present with normal brain MRI results.[158] Increases in volume of brain MRI lesions in patients with isolated syndromes, such as optic neuritis, in the first 5 years correlate only moderately with the degree of long-term disability; therefore, the volume of lesions should not be used alone as a basis for decisions about the use of disease-modifying treatment.[156]

Table 1.2. Treatment recommendations of the Optic Neuritis Treatment Trial

- Corticosteroid treatment should be considered when the brain MRI scan reveals multiple abnormalities consistent with MS.
- Methylprednisolone 250 mg IV should be administered to patients with optic neuritis over a 30-min period every 6 h for a total of 12 doses, or 1 g IV methylprednisolone in one dose over 1 h each day for 3 consecutive days, followed by a prednisone taper at 1 mg/kg/day orally for 11 days. Prednisone should be tapered to 20 mg on day 15 and to 10 mg on days 16 and 18. There are no current studies to demonstrate a clinically significant difference between administering IV methylprednisolone four times a day and giving it all in one dose.
- IV methylprednisolone decreases the incidence of more neurological deficits within the 2 years after treatment, especially in patients who had initial abnormal brain MRI scans.
- IV methylprednisolone does not improve the ultimate visual outcome.

Source: Optic Neuritis Treatment Trial.[198–200]

Intravenous Immunoglobulin

Other treatments, such as intravenous immunoglobulin (IVIG) and retrobulbar steroids, were reported to improve visual acuity in patients who had CDMS with optic neuritis, but no definite conclusions for treatment guidelines could be reached from these small, uncontrolled studies.[202–204] Although IVIG had been demonstrated to have some therapeutic benefit for other demyelinating diseases, such as chronic inflammatory demyelinating polyneuropathy,[202,203] Noseworthy et al. recently found that IVIG did not reverse the chronic visual loss in patients with optic neuritis.[204]

Plasmapheresis

Plasmapheresis is not commonly used for the treatment of optic neuritis. In a recent study of 10 patients treated with plasma exchange for acute, severe optic neuritis unresponsive to previous high-dose IV glucocorticoids,[205] 7 patients experienced visual improvement. On follow-up, 3 patients continued to improve, 2 were stable, and 2 experienced worsening of vision. Plasmapheresis may have a role as "rescue therapy" for patients with a severe attack of optic neuritis.

Interferon Beta-1a

Based upon recent results of the Controlled High-Risk Subjects Avonex Multiple Sclerosis Prevention Study (CHAMPS),[206] patients who received interferon beta-1a at the time of a first

demyelinating event, such as optic neuritis, had a relative reduction in the volume of brain lesions, fewer new or enlarging lesions, and fewer gadolinium-enhancing lesions at 18 months. These patients also had a significantly lower cumulative probability of developing CDMS over the 3-year period of follow-up. The study strongly suggests that long-term clinical benefits with this treatment can be achieved by preventing or delaying a second attack of MS and reducing the progression of CNS demyelination as demonstrated on MRI scans of the brain.[207] Based on the results of the CHAMPS trial, some neuro-ophthalmologists in the United States recommend initiating interferon beta-1a (-β-1a) in patients who present with a first demyelinating event, such as optic neuritis. These patients must also have two or more clinically silent lesions in the brain that are at least 3 mm in diameter on MRI scans and that are characteristic of MS, such that at least one lesion must be periventricular or ovoid.[207,208]

In the extension of the CHAMPS study, CHAMPIONS,[208] patients initially randomized to interferon-β-1a had a 35% less chance of conversion to CDMS over a 5-year period. The placebo group who then started interferon-β-1a at 2.5 years still had twice the relapse rate when compared to the treated arm in years 2.5 and 5.

In the BENEFIT (Betaseron in Newly Emerging MS for Initial Treatment) study,[209] interferon-β-1b reduced the risk of progression to CDMS by 69% compared to 85% (46% reduction by proportional hazards regression) in placebo after 2 years. Treated optic neuritis patients were less likely to develop newly active brain MS lesions at 12 and 24 months compared to placebo.

After following patients in the ONTT for the past 10 years, those who developed CDMS following an initial episode of optic neuritis had a relatively benign course. Fifty-six percent of patients with greater than or equal to one MS lesion converted to CDMS (the second lesion not including the fellow eye developing optic neuritis). Only 22% with a normal MRI converted.[157] Neurological disability was mild in that two-thirds of the patients with CDMS had an Expanded Disability Status Scale (EDSS) score lower than 3.0, whereas severe disability with EDSS score of greater than 6.0 was present in less than 20% of patients.[210] In contrast to the results of Brex et al.[211] in which the number of lesions shown on baseline MR imaging was significantly correlated with the degree of disability after 10 years, the ONTT data revealed moderate or severe disability in 29% of patients with no lesions on baseline brain MRI and in 38% of patients with one or more lesions. Therefore, the results of the baseline brain MRI were not useful in predicting later disability in patients who presented with optic neuritis.[212]

After more than 10 years of follow-up, the ONTT cohort also revealed that a subset of patients with monosymptomatic optic neuritis manifested neither clinical signs nor MRI evidence of demyelination. Not all patients with optic neuritis develop MS. MRI signal abnormalities may also accumulate without causing any clinical manifestations of MS even after more than a decade.[212]

Although some may consider the initiation of immunomodulatory agents in patients at risk of developing MS presenting with optic neuritis expensive and controversial at this time, the weight of the evidence from recent clinical trials support their use early and aggressively to delay the progression of disability.[213] Patients who present initially with optic neuritis in association with other MS symptoms are at greater risk of progressing to CDMS.[212] Although patients with optic neuritis recover their vision, various degrees of cognitive, motor, and sensory deficits accumulate with each exacerbation of MS, leading to permanent neurological disability. The cost of interferon-β-1a must be weighed against the cost of long-term disability. The most frequently reported adverse reactions resulting in discontinuation or dosage adjustment of the drug are injection site disorders, influenza-like symptoms, depression, and elevation of liver enzymes.[214] Data analyzed by Patten and Metz in the SPECTRIMS Trial[215] showed no significant difference in depression ratings before and after administration of interferon-β-1a at 22- and 44-μm three times a week in patients with secondary progressive MS. According to the study by Feinstein et al.,[216]

antidepressant medication given to the 21% of relapsing-remitting MS patients (n = 40) diagnosed with depression before treatment with interferon-β-1b had experienced an overall decrease in depression to 6% at 12 months. Because the lifetime prevalence of depression in MS itself is approximately 40% to 60%,[217] psychiatric complications of MS should be treated aggressively with medications and/or mental health counseling. The decision on whether to start immunomodulatory agents after the first attack of optic neuritis in patients at risk for progressing to CDMS should be based upon consideration of the risks and benefits of the medication and the cost of treatment.

Neuromyelitis Optica

Optic neuritis is an inflammatory demyelinating syndrome of the CNS. It may occur in isolation or as part of multiple sclerosis or neuromyelitis optica (NMO) or Devic's disease.[218,219]

Epidemiology

NMO predominately affects women in 80% to 90% of cases with a median age of onset in the late forties, which is about 10 years later than for MS.[219] Most NMO patients are Caucasians living in North America, but in other parts of the world NMO may be more prevalent in Asians and Africans.[219] Although familial cases have been reported,[220,221] NMO is usually a sporadic disease. In contrast to MS, NMO is not associated with the HLA-DPB1*0501 allele.[223–225]

Diagnosis

The diagnosis of NMO comprises unilateral or bilateral optic neuritis and myelitis without clinical evidence of demyelination in the cerebral white matter. The course of NMO is relapsing-remitting. Although very severe attacks suggest NMO, there is substantial overlap in clinical severity between NMO and MS. Diagnostic evidence that distinguishes NMO from MS includes lack of CSF oligoclonal banding and immunoglobulin abnormalities and lack of autoimmune markers such as ANA, extractable nuclear antigen (ENA), and thyroid autoantibodies.[225] In a study of CSF,[226] oligoclonal bands were detected in 97% (399 of 411) of MS patients and did not disappear. Oligoclonal bands were detected in 27% (3 of 11) of patients and disappeared in all cases. The absence of CSF IgG-1 responses in patients with relapsing NMO may suggest less Th1 immunity and may also explain the low frequency of oligoclonal IgG bands in NMO patients.[227] During a relapse of NMO, CSF pleocytosis and increased CSF protein may be observed. The CSF may have polymorphonuclear lymphocytosis of more than 50 leukocytes/mm^3. Between relapses, the CSF is usually normal.[228] Overall, MRI of the brain and spinal cord is most useful in differentiating NMO from MS. The brain MRI is usually normal (except for possible findings of optic neuritis) or may have a few punctuate nonspecific abnormalities that do not fulfill the radiologic criteria for MS. The spinal cord MRI often reveals a contiguous, longitudinally extensive, gadolinium-enhancing cord lesion that extends over three or more vertebral segments, unlike the shorter cord lesions in MS. The criteria are now being revised to require NMO-IgG seropositivity.[229] The exact specificity of these revised criteria for discrimination of NMO from MS is unclear at this time. The criterion of a negative brain MRI is also being questioned, as asymptomatic and symptomatic lesions develop in patients with a well-established diagnosis of NMO. In another study of 60 NMO patients who fulfilled the 1999 NMO criteria by Wingerchuck et al.,[219] 10% MS-like lesions and 8% had brainstem lesions atypical for MS. Although most lesions were asymptomatic, some were mildly symptomatic. Magnetization transfer (MT) ratio also reveals early abnormalities in normal-appearing brain of NMO patients. Reduced and mean diffusivity is increased in the normal-appearing white and gray matter of patients with NMO.[230]

An indirect immunofluorescence assay that is specific for NMO is the anti-MOG antibody. This IgG marker of NMO binds to the aquaporin-4 water channel, a component of the

dystroglycan protein complex located in astrocytic foot processes at the blood–brain barrier.[229] NMO may represent a novel autoimmune channelopathy.[231] This marker has an approximate 75% sensitivity and greater than 90% specificity for NMO. Approximately 60% of patients with Japanese optico-spinal MS, relapsing transverse myelitis, and relapsing optic neuritis with negative brain MRI are seropositive for NMO-IgG. These data suggest that these disorders represent the same disease or a forme fruste of NMO.[229,231]

Clinical Course

In a retrospective study of 1274 patients with optic neuritis by Pirko et al.,[186] the 10-year conversion rate to MS was 29.8% and to NMO 12.5%. Based upon data from several studies,[232–236] the cumulative conversion rate tends to increase most rapidly in the first 10 years, after which it continues to rise, albeit more slowly. More severe visual loss occurred in those who converted to NMO than to MS. In NMO converters, subsequent relapses also tended to occur earlier than in MS converters or nonconverters.[186]

The course of NMO involves stepwise accumulation of disability because of poor recovery with each relapse. Within 5 years, greater than 50% of relapsing NMO patients have visual acuity of worse than 20/200 or require at least some ambulatory assistance.[219,237]

Although NMO is a monophasic disorder, the relapsing form is more common and occurs in about 90% of cases.[219] Predictive factors that may increase the risk of developing relapsing NMO include the following: (1) first interattack interval is several weeks or more in length; (2) female gender; and (3) better motor recovery after the first myelitis event.[237] Therefore, patients who meet the criteria for NMO and who have a longer interval between the first and second attacks will likely develop relapsing disease. These patients require preventive therapy to decrease disability.

Pathophysiology

NMO is associated with a major humoral immune response (particularly anti-MOG IgM production) and eosinophil activation present exclusively in CSF.[238] Evidence that supports a humoral immune mechanism in NMO includes the following: (1) coexisting systemic autoimmune disorders or autoimmune seropositivity; (2) IgG deposition and activated complement in spinal cord lesions; (3) excellent response to plasma exchange; (4) discovery of NMO-specific IgG autoantibody; and (5) analogy with myelin oligodendrocyte glycoprotein-associated experimental allergic encephalomyelitis.[239]

Treatment

For acute relapses of NMO, IV methylprednisolone 1000 mg/day for 5 consecutive days followed by oral prednisone taper is recommended. Corticosteroids help stabilize or improve function within 1 to 5 days in most patients.[239]

For the prevention of relapses, the combination of azathioprine and prednisone can be used for relapsing NMO patients who do not need immediate induction therapy because they have not had recent clusters of severe attacks or have been free of relapses for several months. These patients often present with severe MS and have not had any improvement with conventional MS therapies. As onset of action of azathioprine can be delayed up to 6 months, prednisone can serve as more immediate immunosuppression. There have been no controlled, double-blind studies on the efficacy of the combination of azathioprine and prednisone, but an uncontrolled, open-label series of seven patients has shown that this combination stabilized relapsing NMO and neurological function improved, as measured by the EDSS.[240] Azathioprine is started at 50 mg/day and increased by 50-mg increments weekly up to a maximal dose of 2.5 to 3 mg/kg/day. Dosage changes are needed if the leukocyte count falls below 3,000/mm^3 or the platelet count decreases below 100,000/mm^3. Prednisone is also started at 1 mg/kg/day, usually up to 60 mg/day to 80 mg/day with the azathioprine. Prednisone can be tapered off when azathioprine reaches its target dose and when clinical symptoms are stable. Some patients may become steroid dependent

and require prednisone 5 mg/day to 15 mg/day to prevent relapses.[239] Some contraindications to this drug are hypersensitivity to the drug itself, pregnancy, and prior exposure to alkylating agents (increased risk of lymphoma). Some side effects include gastrointestinal problems, rash, drug fever, hepatotoxicity, infection leukopenia, anemia, thrombocytopenia, pancreatitis, and alopecia.[239]

For patients who cannot tolerate azathioprine and who do not require immediate-onset therapy, mycophenolate mofetil is another option. It suppresses B- and T-cell proliferation but does not affect hemopoiesis and neutrophil count and activity. It also does not cause gastrointestinal side effects as does azathioprine. For patients with thiopurine methyltransferase deficiency, mycophenolate mofetil may be a better treatment choice. The onset of action is not faster than azathioprine. Mycophenolate mofetil is started at 500 mg twice daily; after 1 week, it is increased to 1000 mg twice daily. Some contraindications to this drug are pregnancy, hypersensitivity to the drug itself, concurrent use of live attenuated vaccines, bone marrow suppression, and hypoxanthine-guanine phosphoribosyl-transferase deficiency.[239]

Rituximab is an anti-CD20 monoclonal antibody that destroys B cells. Because NMO is a B-cell-mediated disorder, this drug has the potential to be beneficial. In a case series of eight patients with worsening NMO, rituximab stabilized the disease for at least several months after its administration. Six of the eight patients were relapse free, and the median attack rate decreased from 2.6 to 0 attacks/patient/year. Seven of the eight patients experienced substantial recovery of neurological function over 1 year of follow-up. The median EDSS score increased from 7.5 to 5.5.[241] Rituximab can be started in patients who have relapsing NMO despite treatment with other immunosuppressive therapies or in patients who need fast-onset induction therapy because of a recent severe relapse. Rituximab is started at 1000 mg intravenously and is given again 2 weeks later. If symptoms continue, rituximab is repeated 1 year later. Contraindications to this drug include type 1 hypersensitivity reactions and hepatitis B infection (may cause reactivation). Some side effects include infusion reactions, such as fever, chills, rigors, nausea, urticaria, angioedema, bronchospasm, and hypotension; and also headache, dizziness, asthenia, rash, and cardiac arrhythmias.[239]

Intravenous immunoglobulin (IVIG) is another treatment option for preventing relapses of NMO, as IVIG is reserved for the treatment of antibody-mediated disorders. No randomized, controlled trials have been done yet on the efficacy of IVIG for NMO. In a report of two relapsing NMO patients who underwent monthly IVIG, they attained complete remission for up to 5.5 years in one patient and for 1 year in the other. IVIG may be effective in preventing relapses in NMO.[242]

Although mitoxantrone has been approved by the U.S. Food and Drug Administration for the treatment of worsening relapsing-remitting or secondary progressive MS,[243,244] it has been used to treat relapsing NMO in some instances. Mitoxantrone inhibits B-cell, T-cell, and macrophage proliferation and impairs antigen presentation. In a report of five patients, four of them with relapsing NMO underwent mitoxantrone treatment that resulted in stabilized disease and improvement on MRI.[245] Mitoxantrone is given at 12 mg/m^2 intravenously every 3 months for up to 2 years for a total of 96 mg/m^2 for relapsing MS. In the small case series, mitoxantrone was started at 12 mg/m^2 and was administered monthly for 6 months followed by three additional treatments at 3-month intervals. Some contraindications to this drug include hypersensitivity to mitoxantrone, hepatic failure, and left ventricular ejection fraction less than 50%. Some side effects are alopecia, diarrhea, nausea, vomiting, headache, myelosuppression, menstrual irregularities, decreased fertility, and urinary tract infections.[239]

Although interferon-β-1b has been used as an immunomodulatory drug for relapsing-remitting MS, a recent randomized, controlled study showed that interferon-β-1b at 250 μg every other day subcutaneously significantly reduced relapse rates [relative reduction of 28.6% ($P = 0.047$)] of relapsing remitting MS and optico-spinal MS. The optico-spinal MS in Japanese patients could be the same disorder as NMO.[246]

Plasmapheresis or plasma exchange (PE) can be used in acute, severe attacks of NMO as "rescue therapy." In a retrospective study of 59 patients with severe attacks of CNS demyelinating disorders, 16.9% had NMO. Sixty percent of the NMO patients had marked functional improvement. These patients improved rapidly following PE, and improvement was sustained.[247] Plasmapheresis is given in exchanges of 55 ml/kg every other day for a total of seven treatments. Some contraindications to this drug include hemodynamic instability, coagulopathy, recent myocardial infarction, severe cardiac disease, thrombocytopenia, and sepsis. Some complications related to insertion of the catheter include thrombotic occlusion of the catheters, hemothorax, pneumothorax, hemorrhage, infection, and venous thrombosis.[239]

Paraneoplastic Optic Neuropathy Syndromes

Paraneoplastic ophthalmologic syndromes are usually retinopathies and rarely optic neuropathies. Only 18 cases of paraneoplastic optic neuropathies have been reported in the literature so far (Table 1.3). Paraneoplastic optic neuropathy is a subacute, progressive, usually bilateral visual loss not associated with pain. The optic disc is normal or edematous and can involve the optic chiasm. Direct compression or infiltration of the optic nerve and acute ischemic optic neuropathy should be ruled out.[248]

Optic neuropathy, as part of a paraneoplastic brainstem or cerebellar syndrome, has been reported in patients with small cell lung carcinoma,[249–254] Hodgkin's and non-Hodgkin's lymphoma,[255,256] neuroblastoma,[257]pancreatic glucagonoma,[258] nasopharyngeal carcinoma,[259] bronchial carcinoma,[260] and, most recently, thymoma[261] (Table 1.3). Most cases present with bilateral optic disc edema and improve with treatment of the cancer (see Table 1.4).[249,251–255,257,258,261]

Neuropathological findings have shown either nonspecific perivascular inflammation,[250,258,260,261] axonal loss, or demyelination of the optic nerve.[250,253,260,261] Pillay et al.[260] reported a case of bilateral visual loss in a 56-year-old man who had bronchial carcinoma; he had bilateral optic disc edema and internuclear ophthalmoplegia. Neuropathological findings revealed that he had secondary demyelination of the medial longitudinal fasciculus with nonspecific lymphocytic infiltration and adhesive arachnoiditis of the optic nerve without any evidence of central nervous system metastasis.[260] In contrast, other cases of paraneoplastic brainstem or cerebellar syndromes showed specific demyelination of the optic nerve, in addition to brainstem gliosis and glial nodule formation and perivascular lymphocytic infiltration without vasculitis affecting small arterioles in the cranial nerve nuclei, the inferior olivary nuclei, the vestibular nuclei, the basis pontis, or the substantia nigra.[250,251,253,260,261]

Optic neuropathy can be associated with a subacute paraneoplastic cerebellar syndrome with an underlying small cell lung carcinoma. Neurological signs may include dysarthria,[251,252] ataxia,[251,261] downbeat nystagmus,[253] horizontal gaze-evoked jerk nystagmus[252] from cerebellar degeneration, and pain, numbness, and absent deep tendon reflexes from a sensory peripheral neuropathy.[252,261] De la Sayette et al.[251] in 1998 identified a novel autoantibody in a paraneoplastic cerebellar syndrome with optic neuropathy that was associated with small cell lung

Table 1.3. Frequency of malignancies associated with paraneoplastic optic neuropathies

Types of malignancies associated with paraneoplastic optic neuropathies	Number of reported cases in the current literature
Lung[253,255–258,268]	6
Bronchial[264]	1
Nasopharyngeal[263]	1
Neuroblastoma[261]	1
Lymphoma[259]	1
—[a]	8/116 patients with lung cancer, thymoma, or other malignancies who tested positive for CRMP-5 developed optic neuropathies[a]

[a]Specific data for individual patients were not available in the study done by Yu et al. 2001.[261]

TABLE 1.4. A review of the treatment outcome in 19 cases of paraneoplastic optic neuropathy from the current literature

Authors and year of reference	Pt. age in years/sex	Type of cancer	Initial VA and/or VF and other eye findings	Type of treatment	Effect of treatment on VA and VF	Length of follow-up
Pillay et al. 1984[260]	56/M	Mixed cell bronchial carcinoma	VA[a] VF[a] Internuclear ophthalmoplegia OU and optic neuritis OS	None	—[a]	Died 9 months later of sepsis; no autopsy done
Waterston and Gilligan 1986[254]	58/M	Small cell lung carcinoma	6/24 OD 6/6 OS Optic neuritis and external ophthalmoplegia OU VF[a]	Prednisolone	6/8 OD 6/6 OS VF[a]	Died 9 months later without clinical evidence of metastases; no autopsy done
Kennedy et al. 1987[257]	21/M	Neuroblastoma	Poor VA OU Disc edema OU Slight enlargement of blind spots OU	Dexamethasone, cyclophosphamide, doxorubicin, VP16-213, alternating with cisplatin, vinblastin, and bleomycin for a total of six courses	Normal vision	5 months
Coppeto et al. 1988[255]	52/M	Chronic lymphomatous meningitis secondary to paranasal sinus lymphoma	CF at 2 feet OD 20/30 OS Optic disc edema OU Generalized constriction of VF	Prednisone and chemotherapy	20/20 OU	Died 14 months later of pneumonia and pleural effusion; no autopsy done
Hoh et al. 1991[259]	31/M	Nasopharyn-geal carcinoma	Poor VA OU Optic neuritis OS Sectorial VF defect OS	ACTH 80 U/day tapered to 10 U/day Prednisolone 30 mg/day tapered to 10 mg/day and retrobulbar methylprednisolone 40 mg injection Prednisolone 20 mg/day then discontinued	6/6 OU Inferior arcuate defect OS Improved VF Scotoma extending to temporal hemianopsia OS and normal VF OD	20 months

(*Continued*)

TABLE 1.4. *Continued*

Authors and year of reference	Pt. age in years/sex	Type of cancer	Initial VA and/or VF and other eye findings	Type of treatment	Effect of treatment on VA and VF	Length of follow-up
				Prednisolone 25 mg/day Optic canal decompression OS Prednisolone 60 mg/day Prednisolone 20 mg/day Prednisolone 15 mg/day	Resolved scotoma OS Inferior altitudinal defect OS Nasal step defect OS Arcuate defect OS Enlarged blind spot OS contiguous with inferior nasal scotoma OS then worsened VF OS	
Malik et al. 1992[253]	63/M	Undifferentiated small cell lung carcinoma with subacute cerebellar degeneration	20/200 OU Cecocentral scotomas and generalized peripheral constriction OU	XRT to mediastinum then chemotherapy	Stable vision after 6 months	Died 20 months later of metastases; confirmed on autopsy
Blumenthal et al. 1998[249]	72/F	Small cell lung carcinoma	Poor VA OU Disc edema OU Severe peripheral constriction OU	Four cycles of chemotherapy	Normal vision	16 months
De la Sayette et al. 1998[251]	62/M	Small cell lung carcinoma	20/25 OD 20/400 OS Central scotomas OU	Cisplatin, etoposide, mediastinal and subclavicular XRT	20/20 OU Normal VF OD and central scotoma OS	23 months
Luiz et al. 1998[252]	59/F	Small cell lung carcinoma	20/30 OD 20/40 OS Disc edema OU Severe peripheral constriction OU	Solumedrol Six cycles of cisplatin and VP16, pulse Solumedrol	Improved vision 20/20 OD 20/25 OS Optic atrophy OU Improved VF	9 months
Yu et al. 2001[261]	—[a]	—[a]	—[a]	—[a]	—[a]	—[a]

Pt., patient; F, female; M, male; VA, visual acuity; VF, visual fields; OD, right; OS, left; OU, both; CF, count fingers; ERG, electroretinogram; XRT, radiation therapy.
[a]Information not available.
[b]Data for individual patients were not available in the study by Yu et al. 2001[261]; 8 of 116 patients with lung cancer, thymoma, or other malignancies who tested positive for CRMP-5 developed optic neuropathies.

carcinoma. This optic neuropathy was identified in only 1 of 12 patients with anti-CV2 antibody-related paraneoplastic syndromes. Anti-CV2, a 66-kDa protein, is the only paraneoplastic autoantibody reported to bind exclusively to oligodendrocytes. The patient was a 62-year-old man who had simultaneously developed a severe cerebellar syndrome and bilateral painless visual loss greater in the left eye than in the right. Funduscopic examination revealed bilateral disc edema, and fluorescein angiography showed marked leakage in the area of the optic discs, also greater in the left eye than in the right. The CV2 antigen was found to be expressed by oligodendrocytes of the cerebellum, brainstem, spinal cord, and optic chiasm. Although a pathological examination was not performed, an immune-mediated secretion or a toxic secretion of cytokines, rather than demyelination, was thought to explain the clinical findings.[251] Nonspecific inflammatory changes and diffuse loss of cerebellar Purkinje cells were seen in previously reported cases involving anti-CV2 antibodies.[262,263]

CRMP-5 is another recently characterized autoantibody associated with paraneoplastic optic neuropathy in small cell lung carcinomas and, rarely, thymomas. This IgG is directed against a 62-kDa neuronal cytoplasmic protein of the collapsin response-mediator family. CRMP-5 is expressed in adult central and peripheral neurons, including synapses, and in small cell lung carcinomas, and rarely in thymomas. The CRMP family of proteins is believed to mediate growth guidance cues during neurogenesis. The CRMP-5 antibody is as frequent as anti-Yo antibody and second in frequency to anti-Hu antibody. The neurological deficits include chorea, cranial neuropathies, peripheral neuropathy, autonomic neuropathy, cerebellar ataxia, subacute dementia, and neuromuscular junction disorders. It is not associated with any specific neurological syndrome. Although 8 of 116 CRMP-5 seropositive patients had optic neuropathy, only 3 of the 8 presented with optic neuropathy at the onset of the illness.[261]

Treatment of the specific cancer in paraneoplastic optic neuropathy patients with chemotherapy and/or radiation therapy resulted in significant visual improvement (see Table 1.3).[249,251–253,255,257] Vision recovered to normal or near normal with improvement of visual fields in 8 of 11 patients (see Table 1.4).[249,251–255,257] Hoh et al.[259] showed that treatment with steroids alone also improved vision in a patient with paraneoplastic optic neuropathy and nasopharyngeal cancer. The visual defects improved with an increase in prednisolone and worsened with its decrease[259] (see Table 1.4).

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Ischemic Optic Neuropathies

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Nonarteritic Anterior Ischemic Optic Neuropathy

Incidence of NAION

Nonarteritic anterior ischemic optic neuropathy (NAION) is a relatively common disorder. The yearly incidence of NAION is 2.3 to 10.2 per 100,000 persons over 50 years of age and 0.5 per 100,000 for all ages.[1] Although NAION usually affects patients older than 50 years,[2,3] it may also occasionally occur in younger patients. In a study by Hayreh et al.[3] of 406 patients with NAION, the mean age of affected patients was 60 ± 14 years, with a range of 11 to 91 years. Eleven percent of the study patients were younger than 45 years, 49% were between 45 and 64 years, and 40% were 65 years or older. There is no sex predilection.[3–5] Caucasians have a smaller cup-to-disc ratio compared to that of African Americans. Most patients affected with NAION are, therefore, Caucasians.[6]

Symptoms and Signs of NAION

In NAION, acute visual loss is usually painless and may present initially with blurred central vision, a visual field defect, or both. In the Ischemic Optic Neuropathy Decompression Trial (IONDT), 42% (174 of 418) developed visual loss within 2 h of awakening, 42% reported that the visual loss occurred later in the day, and the remainder could not recall the time of visual loss.[4] In the IONDT, 10% (17/167) of patients reported mild retrobulbar or retro-orbital discomfort at the time of visual loss. Pain associated with eye movement, such as that seen in optic neuritis, is not considered a typical feature in NAION.[4]

About half the patients in the IONDT had initial visual acuity better than 20/64 and were younger (less than 65 years), with a lower incidence of diabetes and hypertension, and 51% (213 of 420) had visual acuity worse than 20/64.[4] The degree of dyschromatopsia and the severity of the afferent papillary defect is usually proportional to the severity of visual acuity loss.[7] An absolute inferior *nasal* field defect is more common than an absolute inferior *altitudinal* defect. The combination of a relative inferior altitudinal defect with an absolute inferior nasal defect is most often observed in NAION.[6] Other types of field defects include central scotomas, arcuate defects, quadrantic defects, generalized constriction of the field, or a combination of these. In a study of 169 patients by Repka et al.,[7] 46% had inferior altitudinal visual field defects, 20% had central defects, 17% had superior altitudinal defects, 8% had inferior arcuate defects, 8% had inferior quadrantic defects, and 1% had unclassified defects.

The optic disc is more often diffusely swollen, rather than segmentally (Figure 2.1),[8] in which the superior aspect of the disc is more involved than the inferior aspect. This pattern of superior or inferior involvement of the disc may be related to the anatomic division of the circle of Zinn–Haller.[9] The disc edema is pale rather than hyperemic, and flame-shaped hemorrhages may also be seen at or near the disc margin.[9]

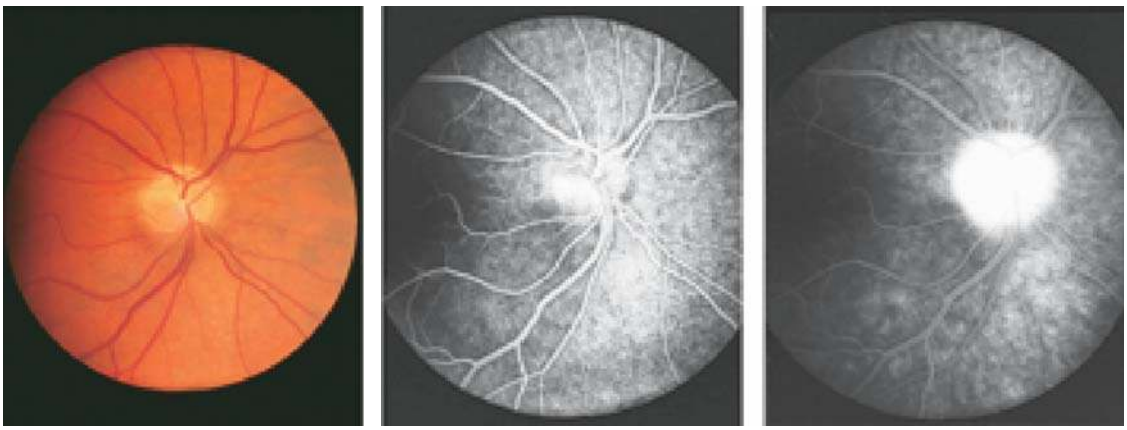

FIGURE 2.1. Acute right nonarteritic anterior ischemic optic neuropathy (NAION). The right optic disc is small with superior disc pallor and inferior disc edema (*left*). The fluoroscein angiogram reveals superior hypofluorescence in the early stages (*middle*) and later leakage (*right*). The peripapillary choroids fills normally. (Reprinted from Spalton et al.,[8] with permission from Elsevier.)

An absent cup or small cup-to-disc ratio is a major predisposing risk factor for the development of NAION. A smaller physiological optic disc cup represents a smaller scleral canal through which the optic nerve exits the eye. Crowding of the optic nerve fibers in the small scleral canal may lead to impairment of axonal transport and decreased laminar circulation.[10]

Arteries in the peripapillary regions are usually focally or diffusely narrowed. In rare instances, hard exudates in the macula rarely may form a hemi-star or, rarely, a complete star figure.[3] After several days or weeks of onset of NAION, focal telangiectatic vessels may develop on the affected disc. It is thought that these changes represent a phenomenon called luxury perfusion, dilation of local blood vessels to allow increased perfusion of the area around the infarcted disc.[2]

The optic disc edema usually resolves within 1 to 2 months after onset. The optic disc then becomes segmentally or diffusely pale. The optic cup rarely enlarges, as in arteritic AION and glaucoma.[10]

Course and Prognosis of NAION

Within a week, most patients experience stabilization of their visual deficits, but visual function may continue to worsen over several days to even weeks after the onset of NAION. In the IONDT, 42% (38 of 89) of the untreated patients also experienced spontaneous improvement of visual acuity by three or more Snellen lines from baseline after 6 months; 44.9% had little or no change, and 12.4% experienced worsening of visual acuity by three or more Snellen lines.[11] After 2 years of follow-up, 31% (27 of 87) of these patients from the IONDT had improvement of three or more lines visual acuity, 47.1% had little or no change, and 21.8% experienced worsening of visual acuity by three or more lines.[12] Therefore, the natural history of visual recovery in NAION was better than previously reported in the literature.[3,7,11]

There are limited data in the literature assessing the extent that visual fields may continue to progress after the onset of NAION. In a study by Arnold et al.,[13] 22.2% (6 of 22) patients had greater than 2 dB increase of mean sensitivity loss, which was measured more than 3 months after onset and may not have captured field loss in the progressive phase of NAION.

Recurrence of NAION in the same eye occurs in less than 5%.[14] It is thought that optic disc atrophy after NAION could decrease crowding of the nerve fibers and reduce the risk of recurrence. Sequential occurrence of NAION is more common because most patients have small cup-to-disc ratios in both eyes

(Figure 2.2).[8] The risk of fellow-eye involvement is 15% within 5 years and is associated with poor baseline visual acuity in the first eye and to diabetes, but not associated with age, sex, smoking history, or aspirin use.[15] In a study by Repka et al.,[7] 24% (20 of 83) of patients with NAION had sequential involvement of the fellow eye. The mean time interval between involvement of the first eye and involvement of the fellow eye was 2.9 years. In the IONDT, 23% (94 of 420) patients had optic disc pallor in the fellow eye, suggestive of a prior episode of NAION. In a study of 4431 patients by Beck et al.,[16] the 2-year cumulative rate of developing NAION in the fellow eye was 15% to 20% at 5 years.

Bilateral simultaneous NAION is rare and is more common in arteritic AION. A subtype of NAION in juvenile diabetes presents simultaneously in both eyes in up to one-third of patients.[17]

Differential Diagnosis of NAION

When atypical features of NAION occur, neuroimaging and other laboratory tests must be performed to rule out alternative diagnoses. Atypical features of NAION include the following: (1) onset at less than 40 years of age, (2) absence of vasculopathic risk factors, (3) no light perception on initial presentation, (3) presence of vitreous cells, and (4) progression of visual field defect and persistent disc edema.[18]

Other types of focal disc ischemia, mimicking NAION, may occur without disc swelling, as in patients with systemic hypertension. Sudden visual field defects, such as small arcuate or paracentral defects, with preserved visual acuity are associated with small nerve fiber layer hemorrhages at the disc margin. This portion of the disc then becomes pale and atrophied to cause a slight increase in the disc cup to mimic glaucomatous cup enlargement, but visual acuity or field defects do not usually progress, as in glaucoma.[19]

The degree of rim pallor, location of rim pallor, and peripapillary retinal artery to vein (A : V) ratio can be useful in distinguishing optic atrophy from NAION or optic neuritis.[20] Disc pallor is often worse in NAION than after optic neuritis. The superior or inferior segment of the disc rim is affected in NAION compared to the temporal-central (papillomacular) or diffuse

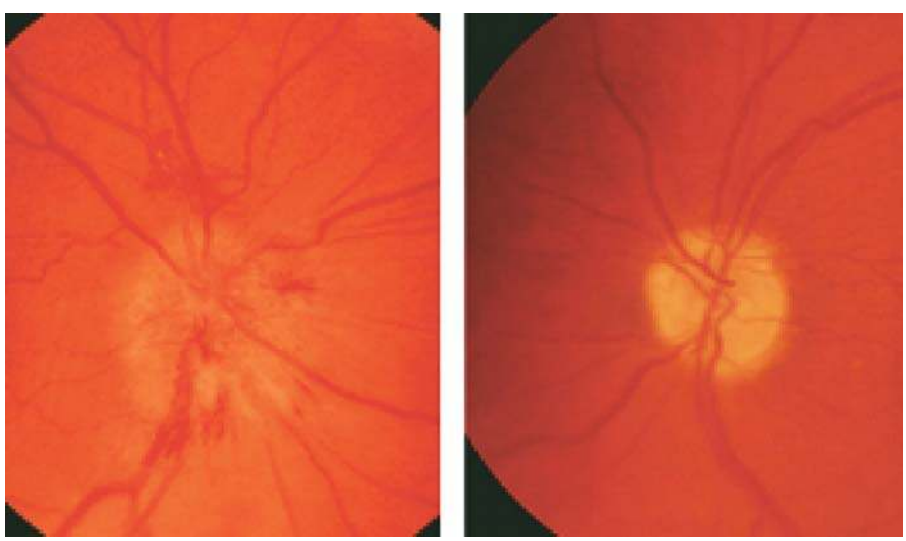

FIGURE 2.2. Bilateral sequential NAION. The right optic disc (*left*) reveals acute disc edema that is most severe inferiorly, with hemorrhage and cotton wool spots. The left optic disc (*right*) is pale secondary to a prior episode of NAION. (Reprinted from Spalton et al.,[8] with permission from Elsevier.)

temporal rim in optic neuritis. The A : V ratio is often lower after NAION compared with that in optic neuritis.[20]

Diagnostic Tests of NAION

On fluorescein angiography, optic disc filling is delayed in patients with NAION, but peripapillary choroidal filling is not always delayed.[21]

Retinal nerve fiber layer thickness, as measured by a scanning laser polarimeter, the GDx nerve fiber layer analyzer (Laser Diagnostic Technologies, Inc., San Diego, CA), is thinner in AION eyes than in healthy eyes and correlates with visual field defects.

Neuroimaging can be used to help differentiate NAION from optic neuritis. In a retrospective study[22] of 64 patients diagnosed as having either NAION or optic neuritis, the optic nerve was abnormal in the clinically affected eye in 31 of the 32 optic neuritis patients but in only 5 of the 32 NAION patients. The 5 NAION patients had increased short (T_1) inversion recovery signal in the affected optic nerve, and 2 had enhancement of the optic nerve.

Risk Factors of NAION

In addition to a small cup-to-disc ratio, other common systemic disorders may be risk factors for the development of NAION. An increased risk of NAION occurs in 47% of patients with hypertension and 24% of patients with diabetes.[4] Diabetes, hypertension, and hypercholesterolemia are more associated with NAION in younger patients less than 50 years of age than in older patients.[2] In the IONDT, 60% of patients had one or more vasculopathic risk factors, including hypertension, diabetes, and tobacco use.[4] In an uncontrolled study of 137 patients, smoking was a significant risk factor for NAION in younger patients compared to nonsmokers.[23] Other studies have shown conflicting data in that hypertension was not found to be significantly more prevalent in patients with NAION than in age-matched controls.[24] Another case-controlled study also did not support smoking as a risk factor for NAION.[24]

Carotid artery stenosis or occlusion is not considered a cause of NAION, but rather there is evidence of widespread atherosclerosis affecting both large and small vessels.[25] In a carotid Duplex scan study with 15 patients with NAION,[26] 11 patients with transient monocular blindness, and 30 age-matched controls, the mean carotid stenosis was not significantly worse in NAION patients (19%) compared to controls (9%), but more severe in patients with transient monocular blindness (77%). Two of the 15 patients with NAION had carotid stenosis greater than 30%, compared with 5 of 30 controls and 10 of 11 patients with transient monocular blindness.

Pathogenesis of NAION

Mechanical and anatomical factors have also been shown to influence the risk of developing NAION. A small cup-to-disc ratio, or a small disc with little or no physiological cupping, implies a small optic disc diameter and smaller scleral canal. Nerve fibers pass through a restricted space in the lamina cribosa and optic disc. The crowding of nerve fibers in this small canal and axoplasmic stasis associated with disc edema are the two factors thought to contribute to anterior disc ischemia. This compressive ischemia induces further stasis of axoplasmic flow, and a vicious cycle of ischemia ultimately ends in disc infarction.[24] Using digital imaging technology to reconstruct serial histopathological sections of an optic nerve affected by NAION, Tesser et al.[27] have shown that the morphology of the NAION infarct appears to be more consistent with a compartment syndrome causing tissue ischemia than a disease of blood vessels. In addition to a small disc size and small physiological cup, anatomic features in a "disk at risk" include elevation of the disc margins by a thick nerve fiber layer and anomalies of blood vessel branching. The sharp 90° turn of the retinal ganglion cell axons entering the lamina cribosa has also been thought to contribute mechanical stress to decrease axoplasmic flow.[28,29]

Vascular and hemodynamic factors are also thought to contribute to the pathogenesis of NAION. There has been no pathological evidence so far showing occlusion of the posterior ciliary arteries in patients with NAION, but

fluorescein angiography has revealed delayed filling of the prelaminar optic disc in the edematous phase before the development of impaired filling associated with atrophy from loss of vasculature.[30] Further studies by Arnold et al.[31,32] showed that delayed prelaminar optic disc filling, appearing later than choroidal and retinal filling, was seen in 76% of patients with acute NAION, compared with no delay in normal controls. No consistent delay in adjacent parapapillary choroidal filling was seen compared to normal controls. The delayed optic disc filling in NAION with normal parapapillary choroidal filling is suggestive of impaired perfusion within the paraoptic branches of the short posterior ciliary arteries supplying the optic disc distal to the branching of the choroidal vessels from the short posterior ciliary arteries. Vascular insufficiency in the paraoptic branches of these short posterior ciliary arteries that supply the laminar and prelaminar regions of the optic disc may result in ischemia and infarction.[33] These short posterior ciliary arteries form the circle of Zinn–Haller to supply the anterior optic nerve in two distinct superior and inferior regions. Hypoperfusion in either of these vascular territories results in corresponding altitudinal defects.[34,35]

Nocturnal hypotension may play a role in the development of NAION. Hayreh et al.,[36] showed that a 25.3% decrease in systolic blood pressure and a 31.2% decrease in diastolic blood pressure occurred in 52 patients with NAION during 24-h ambulatory blood pressure monitoring. No control patients were monitored, but the age-matched normal population for nocturnal diastolic reduction was only 7% to 21%. Patients with worsening field defects from NAION and who were taking antihypertensive medications had even lower nocturnal diastolic reductions. Another study on 24 patients by Landau et al.[37] showed a mean systolic blood pressure reduction of 11% and a mean diastolic blood pressure reduction of 18% in patients with NAION, compared to controls, who had 13% and 18%, respectively. No significant difference was seen, but a substantially slower rise in blood pressure during the morning was observed in patients with NAION when compared to normal controls. Therefore, the role of nocturnal hypotension in the development of NAION remains unclear at this time.

Vasospasm from ineffective vascular autoregulation and/or structural changes in vessels causing narrowing may result in increased vascular resistance that then leads to reduced perfusion pressure in the optic nerve head.[9,38] Autoregulatory mechanisms may be impaired by arteriosclerosis, vasospasm, or antihypertensive medications, such as beta-blockers. In studies by Hayreh,[39] serotonin-induced vasoconstriction was observed in central retinal arteries and posterior ciliary arteries of monkeys who had atherosclerosis. This abnormal vasoconstriction induced by endogenous serotonin released during platelet aggregation within atherosclerotic plaques was mediated by endothelial-derived vasoactive agents. Hayreh et al.[36] proposed that this vasoconstriction could cause impaired autoregulation to result in hypoperfusion of the optic nerve head. These endogenous vasoactive agents, such as endothelin-1 and calcium ions, have been shown to cause hypoperfusion in the optic nerve head, as measured by laser Doppler flowmetry.[40] The ischemia was reversible with a calcium channel blocker. Another study showed that repeated intravitreal injections of endothelin-1 in rabbits reduced blood flow to the optic nerve head to cause axonal loss.[41]

Treatment of NAION

Surgical decompression of the optic nerve and medical treatments, including anticoagulants,[42] diphenylhydantoin,[43] levodopa,[44] sub-Tenon's injections of vasodilators,[42] intravenous norepinephrine,[45,46] thrombolytic agents and stellate ganglion blocks,[47] corticosteroids,[48] aspirin,[49] and heparin-induced low-density lipoprotein/fibrinogen precipitation or hemodilution,[50] have not been proven to be effective. Optic nerve decompression surgery (ONDS) failed to show any long-term benefit in patients with NAION, because the rate of improvement after ONDS was similar to the rate of spontaneous improvement, and this procedure had no influence on the clinical course of NAION.[51] In the IONDT, 23.9% of patients undergoing surgery had a significantly greater risk of losing three or more

lines of Snellen visual acuity at 6 months compared to 12.4% of the patients without surgery.[11] The IONDT Research Group finally recommended that ONDS should not be performed for acute NAION.[12]

Although no proven treatments are available for NAION at this time, aspirin may have a role in decreasing the risk of recurrence of NAION in the second eye after NAION in the first eye. In a retrospective, uncontrolled study by Beck et al.,[52] the 2-year cumulative probability of NAION in the second eye was 7% in the 153 patients taking aspirin and 15% in the 278 patients not taking aspirin. The 5-year cumulative probabilities in both groups were 17% and 20%, respectively. Although the long-term benefit of aspirin to prevent NAION in the second eye was minimal, the short-term, 2-year, benefit of taking aspirin appeared significant. In the follow-up study of the IONDT, NAION in the second eye occurred in 14.7% of IONDT patients over approximately 5 years. This rate of recurrence of NAION did not appear to be influenced by aspirin use.[53]

Although the neuroprotective effects of topical brimonidine were promising in animal studies, 0.2% brimonidine tartrate proved unsuccessful in patients with NAION.[54] In a 3-month double-blind, placebo-controlled, randomized multicenter trial of 36 patients older than 40 years of age with first-eye involvement of NAION within the first week after visual loss, the final visual acuity did not show any statistically significant difference by treatment. Nonsignificant trends for improved visual fields were noted in the brimonidine group. No serious adverse events occurred.

Levodopa and carbidopa have been shown in some studies to be effective in improving visual acuity visual fields after NAION. In a prospective, randomized, double-blinded, placebo-controlled trial of 20 patients with NAION of 30 months mean duration,[44] the patients treated with levodopa/carbidopa had a mean visual improvement of 7.5 letters from baseline compared with the placebo group. Three patients had a doubling of the visual angle as denoted by a gain of at least 15 letters. Color vision did not significantly change. In another study of 37 patients with NAION of less than 45 days duration,[55] 76.9% (10 of 13) of patients who received levodopa/carbidopa with visual acuity of 20/40 or worse at baseline had improved visual acuity at 6 months. None of the 18 patients treated with levodopa/carbidopa had worsened visual acuity. In contrast, 30% (3 of 10) of control patients with 20/40 or worse at baseline had improved visual acuity at 6 months, and 16.3% (3 of 19) of control patients had worsened visual acuity. Although levodopa/carbidopa appears beneficial in the treatment of NAION, another study of 24 patients who were randomized to receive levodopa/carbidopa or placebo[56] showed that the drug had no therapeutic effect on the visual recovery of patients with NAION. Side effects of levodopa, such as dizziness, orthostatic hypotension, vomiting, and cardiac arrhythmia, were observed.

Recent interest in using hyperbaric oxygen therapy for ischemic conditions has given rise to the possibility of its application to NAION. Although several studies by Bojic et al.[57–59] have shown promising results in patients with NAION with hyperbaric oxygen, data regarding the benefits of hyperbaric oxygen for NAION have been controversial. In the study of 20 patients by Arnold et al.,[60] no significant improvement in visual acuity or visual field after treatment with 100% oxygen at 2.0 atmospheres of pressure.

Heparin-induced extracorporeal low-density lipoprotein (LDL)/fibrinogen precipitation (HELP) eliminates selectively fibrinogen, LDL, cholesterol, triglycerides, and LP(a) from blood plasma using extracorporeal circulation. The reduction of fibrinogen and LDL by about 50% after only one procedure can be safe and more effective than hemodilution in improving the hemorrheological and the functional situation in NAION. LDL apheresis was tried successfully in a 64-year-old patient with bilateral sequential NAION who had hypercholesterolemia as his only risk factor. After undergoing three sessions of LDL apheresis, the scotomas reduced in size after each session until it remained stable at 6 months. His best corrected vision improved from 2/10 to 6/10 after the third session of treatment. LDL cholesterol and fibrinogen decreased after the third session from 239 to 31 mg/dL and from 289 to 92 mg/dL,

respectively. Whether this man experienced spontaneously visual recovery coincidental with LDL apheresis is unclear.[53]

Transvitreal optic neurotomy in the treatment of NAION involves relaxation of the scleral ring of the prelaminar and laminar regions of the optic nerve head to reduce constriction of underperfused nerve fibers. This scleral outlet compartment syndrome is thought to lead to necrosis of edematous nerve fibers.[61] In a report by Soheilian et al.,[61] seven patients with severe visual loss of less than 20/800 from NAION underwent transvitreal optic neurotomy. Visual acuity improved in six of seven patients. The mean preoperative visual acuity was 20/2400 and the mean postoperative visual acuity was 20/250, with an average of 10 lines of improvement. Visual fields improved in two patients who had enough visual acuity to undergo perimetry. Other patients with severe visual loss could not perform preoperative or postoperative visual field testing.

Anterior Ischemic Optic Neuropathy in Other Clinical Settings

Although NAION usually occurs in older patients with vasculopathic risk factors, anterior ischemic optic neuropathy may also occur in various other clinical settings.

Diabetic Papillopathy

Diabetic papillopathy is an atypical form of NAION.[62] In patients with juvenile diabetes, transient unilateral or bilateral optic disc edema often develops with mild or absent visual symptoms. Blind spot enlargement is more commonly seen than an arcuate field defect. Although these field defects may persist, visual acuity usually improves as the disc edema resolves.[63,64,65] The dilated, telangiectatic vessels on the disc, mimicking neovascularization,[65] disappear as disc edema resolves. The formation of these vessels is thought to be related to the luxury perfusion phenomenon described after typical NAION.[66] Diabetic papillopathy may develop in patients with or without diabetic retinopathy. Typical NAION with true disc neovascularization may also occur in patients with juvenile diabetes.[67]

Diabetic papillopathy may also be seen in patients with adult-onset diabetes mellitus.[68,69] In a study of 19 patients with diabetic papillopathy,[69] the mean age of onset was 50 years of age and 33% had type II diabetes mellitus. Hyperemic disc edema resolved within 3.7 months. Seventy percent of eyes had macular edema and 52% of eyes had capillary nonperfusion on fluorescein angiography. Eighty-nine percent (34 of 38) of eyes had a final visual acuity of 20/50 or better. Decreased visual acuity was related to macular edema.

Similar to typical NAION, a small cup-to-disc ratio is a risk factor for the development of diabetic papillopathy.[69] In a study of 27 eyes with diabetic papillopathy,[69] 63% (17 of 27) had cup-to-disc ratios of 0.1, which was significantly higher than normal controls. Diabetic papillopathy can even precede the development of typical NAION. In a report by Sato et al.,[70] a 58-year-old woman with diabetes mellitus and small cup-to-disc ratios developed bilateral optic disc edema. Her left inferior altitudinal defect and hypoperfusion in the superior segment of the left optic disc on the early phase of the fluoroscein angiogram were consistent with left NAION. Her right eye then developed similar findings. Although her vision recovered slightly, the visual field defects remained in both eyes.

NAION Associated with Optic Disc Drusen

NAION has been associated with optic disc drusen, which could cause compression of the optic nerve fibers and decrease disc circulation.[71] Based on a review of 20 patients who experienced an episode of AION in an eye with optic disc drusen,[72] the mean age of the patients was 49.4 years, with a range of 18 to 69 years. Fifty percent had vascular risk factors. Three patients reported episodes of transient visual loss before their permanent field defects. Sixty-two percent of eyes had 20/60 or better. Seventy-nine percent had an altitudinal or arcuate field defect, and 21% had a cecocentral scotoma. Final visual acuity was 20/40 or better in 62%

of eyes and 20/200 or worse in 14% of eyes. Patients with optic disc drusen-related NAION were younger than those with NAION, were more likely to report preceding episodes of transient visual obscuration, and had a better visual acuity outcome. Vascular risk factors, pattern of field defects, and occurrence of a subsequent similar event in the fellow eye were similar to those with NAION not related to optic disc drusen.

Chlamydia in AION

Increasing evidence links *Chlamydia pneumoniae* with atherosclerosis and other vascular disorders. In a retrospective case-controlled study of 71 patients with NAION and 71 controls matched for age and gender,[73] patients with NAION had significantly higher IgG antibody titers to *C. pneumoniae*, an IgG titer of 1:128 or greater in 29 patients compared to 15 controls. The odds ratio for patients with an IgG titer of 1:128 or greater was 2.56 with a 95% confidence interval of 1.2 to 5.5. Adjustment for hypertension, diabetes mellitus, and myocardial infarction resulted in an odds ratio of 3.48 with a 95% confidence interval of 1.3 to 9.6. Although this study suggested that elevated titers of IgG antibodies to *C. pneumoniae* were associated with NAION, another study of 14 patients with NAION revealed that *C. pneumoniae* IgA, IgG, and IgM titers were not significantly different than those of age- and sex-matched controls. No specific *C. pneumoniae* nucleic acid sequences were detected in the AION patients or in the controls.[74] This study did not support the association of AION with previous *C. pneumoniae* infection. *C. pneumoniae* may play a role in initiating atherosclerosis, but its role in mediating specific vascular disorders is still unclear.

Shock-Induced AION

Shock-induced anterior ischemic optic neuropathy (SIAION) is associated with anemia and hypotension.[75,76] Acute visual loss after spontaneous hemorrhage usually affects patients between 40 and 60 years of age.[77] Bilateral visual loss often occurs within 48 h after the onset of hemorrhage in about half of patients and may present up to 10 days later in 40% of patients.[76] Unilateral visual loss occurs in about 12% of patients.[77]

A small cup-to-disc ratio, or "disk at risk," may be a risk factor for developing SIAION.[78,79] In a review of fundus photos from 19 patients with SIAION,[79] 14 patients had optic disc morphology typical of acute NAION. The affected optic disc was diffusely pallid and edematous and small. Most had small or absent central cups. Peripapillary hemorrhages were occasionally seen. The fellow unaffected eye also often had a small cup-to-disc ratio.

After acute spontaneous hemorrhage, about 50% of patients with NAION experience some visual recovery, but only 10% to 15% recover completely.[77,80–84] In most documented cases of spontaneous hemorrhage, the hemoglobin is less than 5.0 g/dL at the time of visual loss.[85]

Hypotension and anemia are both risk factors for developing NAION in uremic patients on dialysis. NAION has been reported more often in chronic uremic adult patients (12) than in uremic children (5) on dialysis.[86,87] Adult uremic patients who developed NAION were usually on dialysis for many years with chronic hypotension that was exacerbated during each dialysis treatment. They presented more often with bilateral, rather than unilateral, acute visual loss during hemodialysis.[88,89] Neither the type of dialysis, hemo- or peritoneal dialysis, nor sex of the patient seemed to have any influence on the occurrence of NAION.[86] Some visual recovery may be possible if the hypotension during dialysis is corrected in a timely manner. Two adult uremic patients have been reported to develop NAION in this setting recovered partial vision, such that the visual acuity in one eye of one of the patients improved from no light perception for several hours to 20/40.[90]

Patients with end-stage renal disease and long-term hemodialysis who develop calcific uremic arteriolopathy can be at risk for developing NAION.[91] In a report by Korzets et al.,[91] two uremic patients presented with hypotension and acute unilateral visual loss. Although they were treated with high-dose steroid therapy, significant vision was not recovered. Their temporal artery biopsies revealed medial

calcification. Hypoperfusion to the optic nerve head can result from a combination of hypotension and calcific arteriolopathy in arteries supplying the optic nerve.

NAION may occur during the perioperative period, including cardiopulmonary bypass,[92–96] aortofemoral bypass,[97] various abdominal procedures,[76,80–85,98] hip surgery,[94] mitral valvulotomy, cholecystectomy,[80] parathyroidectomy,[99] lumbar spine surgery,[97,100,101] and after coronary angiography.[102] In a review of 30 patients with perioperative ischemic optic neuropathy,[100] 17 were of the anterior type. NAION was associated with hypotension and/or anemia and occurred mostly after coronary bypass surgery. The mean hemoglobin level decreased by 42% (from 143 to 83 g/L) in 4 of the patients during the perioperative period. NAION associated with lumbar surgery was thought to result from the deliberate reduction of intraoperative blood pressure to reduce bleeding and the reluctance to transfuse because of the risk of human immunodeficiency virus (HIV) type 1 transmission from contaminated blood. Twenty-eight of the patients in this study were older than 40 years of age and had the vascular risk factors for AION, such as hypertension, coronary artery disease, diabetes mellitus, and a history of smoking. Bilateral AION occurred in 18 of 30 patients. More than 50% had visual acuity worse than 20/100 with little or no visual recovery. Most patients presented with optic disc edema at the time of initial visual loss, while others developed delayed disc edema several days later.

In a study of six patients with perioperative ischemic optic neuropathy,[97] three had the anterior type. Two patients had bilateral AION and one had unilateral AION. Their optic discs were small with little or no central cup. They all had hemoglobin levels less than 80 g/L for 30 min to 72 h with decreased mean blood pressure between 24% and 46% of preoperative levels for more than 15 to 120 min.

Because 10% to 15% of cardiac procedures are currently performed without cardiopulmonary bypass to reduce morbidity, two patients who underwent off-pump cardiac surgery developed postoperative NAION.[102] Potential risk factors in the second patient were severe anemia, new-onset atrial fibrillation with rapid ventricular rate, hypotension postoperatively, a small optic disc, uncontrolled diabetes mellitus, and a past medical history of hypertension and coronary artery disease.

NAION has also been reported to occur after large-volume liposuction in two patients.[103,104]

NAION and Elevated Intraocular Pressure

It is unclear whether elevated intraocular pressure (IOP) may play a role in the development of NAION. Studies in the past 36 years have revealed conflicting data. Elevated IOP and glaucoma were associated with NAION.[105,106] In a study by Katz,[106] the mean peak diurnal IOP was greater in 16 patients with NAION than in the 15 normal controls. It was suggested that a transient increase of IOP could lead to ischemia of the optic nerve head because of a decrease in perfusion pressure below a threshold level. In a study by Hayreh et al.,[107] the IOP was not elevated in patients with NAION compared to patients with open-angle glaucoma and normal-tension glaucoma. In another study of 137 patients with NAION by Chung et al.,[108] the mean IOP was 16.2 mmHg, which was similar to the IOP expected in the general population.[109] It is still unclear whether elevated IOP is associated with the development of NAION.

In a review by Williams et al.,[110] some patients experienced both AION and PION from orbital or ocular compression during the face-down position in surgery. Increased intraocular pressure and decreased perfusion pressure in the optic nerve head during cervical spine surgery are thought to increase the risk of developing NAION. In a report by Abraham et al.,[111] on an uneventful surgery for atlanto-axial dislocation in the prone position, a 32-year-old man developed sudden unilateral painless visual loss immediately postoperatively. He recovered his visual acuity completely in 1 month, but his optic disc pallor, inferior altitudinal defect, and color deficit persisted. No evidence of intraoperative anemia, hypotension, or vasculopathic risk factors was noted. His NAION was thought to be related to surgery in a prolonged prone

position with his face on a malpositioned horseshoe headrest, which could potentially increase the intraocular pressure and decrease the perfusion pressure of the optic nerve head.

NAION and Chronic Anemias

In addition to hypoperfusion from acute hypotension and hemorrhagic-related anemia, chronic nutritional anemia may be a predisposing factor to NAION. NAION has been reported in severe folate deficiency anemia.[112] It is hypothesized that a low hematocrit can reduce the oxygen-carrying capacity of blood to lead to NAION.[113] A left NAION developed in a 37-year-old man with a hematocrit of 13.9% and hemoglobin of 4.5, with a mean corpuscular volume of 125, corrected reticulocyte count of 0.5%, and a folate level of 0.9 ng/mL (normal, greater than 1.8 ng/mL). The cup-to-disc ratio was not reported. Very low hemoglobin levels may decrease oxygen delivery to the prelaminar optic nerve to cause NAION. Even mild iron deficiency anemia has been associated with NAION. In a report by Kacer et al.,[114] a 50-year-old woman developed unilateral NAION that was related to her underlying iron deficiency anemia with a hemoglobin of 7.3 g/dL and hematocrit of 25%.

NAION and Coagulopathies

NAION has been associated with coagulopathies, such as antiphospholipid antibody syndrome, protein C and S deficiencies, antithrombin deficiency, tissue plasminogen activator deficiency, heterozygous factor V Leiden mutation, and methyltetrahydrofolate reductase mutations.

In a study by Acheson and Sanders,[115] seven patients developed NAION associated with a prothrombotic state. The total number of patients tested was not reported. Two patients had reduced levels of protein C, one of protein S, one of antithrombin III, and one of tissue-plasminogen activator (t-PA). Two others were found to have the lupus anticoagulant. Bilateral visual loss occurred in six of seven patients and recurrent or progressive visual loss occurred in the same eye in four of seven patients. Two patients presented were less than 30 years of age. Many of these patients also had vasculopathic risk factors of hypertension, diabetes, and smoking. A subgroup of patients less than 40 years of age and recurrent episodes of visual loss may have NAION that needs to be treated with anticoagulants.

In the retrospective case-controlled study by Salomon et al.,[25] 61 patients with NAION were tested for protein C, protein S, antithrombin III, lupus anticoagulant, Factor V, Factor II, and methyleneterahydrofolate reductase (MTHFR C677T). None of the genetic or acquired thrombophilic markers was a significant risk factor for NAION. Ischemic cardiac disease, hypercholesterolemia, and diabetes mellitus were deemed risk factors for NAION with odds ratios of 2.9 (95% confidence interval, 1.3–6.4), 2.6 (95% confidence interval, 1.2–5.5), and 2.3 (95% confidence interval, 1.1–4.8). Ischemic cardiac disease and hypercholesterolemia had an additive risk for NAION with a combined odds ratio of 4.5 (95% confidence interval, 1.4–14.5). This study suggested that prothrombotic factors did not play a significant role in NAION, but vasculopathic factors were more important.

In a study of 25 patients with NAION by Nagy et al.,[116] 24% (6 of 25) had activated protein C (APC) resistance secondary to the heterozygous factor V Leiden mutation compared to only 5.9% in the control group. Odds ratio calculations showed that patients with factor V Leiden mutation were at a significantly increased risk of developing NAION than control patients.

Patients with NAION may also have impairment of homocysteine metabolism.[117] Mild hyperhomocysteinemia is considered an independent risk factor for atherothrombotic disease, such as NAION. In a study by Kawasaki et al.,[118] elevated plasma homocysteine was found in 17% (2 of 12) of patients who had bilateral sequential NAION. Neither of these 2 patients had hypertension or had a history of smoking. One of them had mild hypercholesterolemia.

NAION can be associated with homozygosity for the C677T MTHFR mutation.[119] In a study of 12 patients with NAION, 58% had at least one gene mutation in the C677T MTHFR, G1691A V Leiden, or G20210A prothrombin gene, compared with 14% in the controls. The sample size

had a power of 85% to detect this case-control difference at alpha = 0.05. Of the 8 women with NAION, 63% first experienced visual loss while taking hormone replacement therapy or during pregnancy with estrogen-induced thrombophilia superimposed upon heritable thrombophilia and hypofibrinolysis. In another study by Weger et al.,[120] however, hyperhomocysteinemia, not the MTHFR C677T mutation, was found to be associated with NAION.

NAION is also associated with a specific platelet polymorphism located on the glycoprotein Ib alpha gene.[121] In this study of 92 patients with NAION, the B allele of glycoprotein Ib alpha with a variable number of tandem repeats (VNTR) was an independent risk factor for NAION, with an odds ratio of 4.25 and a 95% confidence interval of 1.67 to 10.82. Fifty-six percent (9 of 16) of patients who had the B allele VNTR developed NAION in the fellow eye compared to only 23.6% (17 of 72) of controls had second-eye involvement. Recurrence of NAION in the fellow eye occurred earlier in patients who had the specific gene polymorphism. The presence of the B allele VNTR of glycoprotein Ib alpha confers a significant risk for NAION and predisposes affected patients to fellow-eye involvement.

A prothrombotic abnormality should be ruled out in a patient who has any of the possible predisposing factors for NAION: (1) history of primary antiphospholipid antibody syndrome or other hypercoagulable states, (2) family history of clotting disorders, (3) absence of vasculopathic risk factors, (4) age of 40 years or less, (5) recurrent episodes of AION in the same eye or in the fellow eye, (6) history of smoking, and (7) use of estrogen-progestin oral contraceptives or replacement estrogen therapy.[122,123]

Laboratory studies should include CBC with differential and platelets, elevated sedimentation rate (ESR), fibrinogen level, PT and aPTT; anticardiolipin IgM and IgG antibodies, lupus anticoagulant, fasting serum level of homocysteine, folate, and vitamin B_{12}. When fasting serum homocysteine is elevated, the folate level is usually low and vitamin B_{12} level shows no significant change.[122]

If prothrombotic abnormalities are present after checking laboratory abnormalities 6 months later, then a hematologist should be consulted for further management.[122]

NAION in Migraine

Patients with classical migraines can occasionally develop NAION during a severe headache.[124–129] Vasospasm is believed to play a role in reducing perfusion to the optic nerve head.[130] In previously reported cases, visual acuity usually improved, but visual field did not. Recurrence of NAION was not observed for up to 2 to 3 years after the initial attack.

NAION can occur in other disorders presenting with migraine, such as cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). In a report by Rufa et al.,[131] a 60-year-old man with diffuse subcortical leukoencephalopathy, tetraparesis, and a family history of stroke presented with acute right visual loss at the age of 27 years. Reevaluation at this later age revealed that his right optic disc atrophy was associated with arteriolar narrowing and decreased right visual acuity. Fluorescein angiography of the right eye revealed persistent peripapillary hypofluorescence with a retinal pigment epithelial window defect in the inferior temporal region. Pattern reversal visual evoked potentials were absent in the right. The left P100 latency was delayed and reduced in amplitude. The diagnosis of CADASIL was confirmed by molecular analysis, in which he was shown to be heterozygous for the C406T mutation on exon 3 of the Notch 3 gene. The possibility of CADASIL should be considered in patients with NAION who do not have typical cardiovascular risk factors but do have a family history of stroke.

NAION and Sleep Apnea Syndrome

Sleep apnea syndrome could play an important role in the pathogenesis of NAION. In a 2002 study by Mojon et al.,[132] 71% (12 of 17) patients with NAION had sleep apnea syndrome. Approximately 75% of patients with NAION experience visual loss upon awakening.[133] It is hypothesized that repetitive prolonged apneas may impair optic nerve head blood flow autoregulation.[134] Impairment of vascular

autoregulation in the optic nerve head may be a result of sleep apnea-related arterial blood pressure fluctuations (episodic nocturnal hypertension or hypotension), arteriosclerosis,[134] and even an imbalance between vasodilators, such as nitric oxide, and vasoconstrictors, such as endothelin.[123] Episodic increased intracranial pressure during apnea[135] may also contribute to decreased circulation in the optic nerve head. In a prospective study of 108 patients with sleep apnea syndrome treated with continuous positive airway pressure (CPAP) between 4 months and 6 years, 1 patient had bilateral sequential NAION and 2 patients had unilateral NAION despite treatment with CPAP.[136] Larger studies are needed to clarify the role of CPAP in preventing NAION.

Arteritic Anterior Ischemic Optic Neuropathy

Incidence of Giant Cell Arteritis

The most common vasculitic disorder that causes AION is giant cell arteritis (GCA). AION is also the most common cause of visual loss in patients with GCA,[137] comprising 71% to 83% of cases.[138,139] Because the incidence of GCA increases with age by about 22 fold from 60 to 90 years of age, more patients older than 65 years are affected by GCA than by NAION. It occurs most commonly in Caucasian women. The yearly incidence is 20 per 100,000 persons more than 50 years of age.[140,141]

Symptoms and Signs of GCA

Besides advanced age, headache, scalp tenderness, jaw claudication, ear pain, myalgia, arthralgia, fatigue, fever, chills, malaise, anorexia, and weight loss are systemic symptoms associated with GCA.[142] More than 20% of patients with positive temporal artery biopsies do not have these systemic symptoms.[143] The risk of permanent visual loss in GCA is increased in patients with transient visual loss and/or jaw claudication and decreased in those with elevated liver enzyme levels and/or constitutional symptoms.[144]

Visual loss in arteritic AION may occur suddenly or may be preceded by transient monocular visual symptoms in 30% of cases or by transient diplopia and amaurosis fugax in 2% to 30% of cases.[143] These episodes of transient ischemia may lead to ischemic optic neuropathy, central or branch retinal arterial occlusion, choroidal infarction, or a combination of any of these structures.

Visual loss is usually unilateral initially, but if untreated, becomes bilateral within days to weeks in 30% of cases.[145] The visual loss is much more severe in patients with arteritic AION than in those with NAION. Approximately 54% of patients with arteritic AION have a visual acuity of count fingers to no light perception, compared to 26% of patients with NAION.[145] In contrast to the hyperemic disc edema in NAION, the optic disc edema in arteritic AION often has a chalky-white appearance that may be complicated by retinal or choroidal ischemia, causing visual loss to be more severe. Cotton wool spots and flame-shaped intraretinal hemorrhages may also be seen in the peripapillary area. Unlike NAION, arteritic AION may occur in discs of any size.

Visual field defect in patients with arteritic NAION may be altitudinal, arcuate, and even more extensive than those with NAION.[145]

Visual loss in arteritic AION is progressive and may affect the fellow eye in 25% to 50% of patients within several days or weeks. As the swelling resolves, the disc becomes pale and the retinal arteries become narrowed. In contrast to NAION, cupping and neuroretinal rim loss can eventually develop in arteritic AION. Although these two disc features are also seen in glaucomatous optic neuropathy, arteritic AION is not associated with an enlargement of parapapillary atrophy.[146]

Pathophysiology of GCA

The inflammation in arteritic AION affects blood vessels that lack an internal elastic lamina. The short posterior ciliary arteries supplying the retrolaminar and laminar regions of the optic disc are most commonly affected. Sectors of choroid ischemia may occur concomitantly

with arteritic AION. The ophthalmic artery, posterior ciliary arteries, and the intraneural central retinal artery are rarely affected to cause orbital ischemia. The severity of permanent loss in visual acuity and visual field is determined by the extent of infarction.[145]

T cells and macrophages infiltrate into the layers of the arterial to directly or indirectly regulate the process of myofibroblast proliferation and matrix deposition. Multinucleated giant cells and macrophages located at the media-intima border produce not only platelet-derived growth factor (PDGF) but also vascular endothelial growth factor (VEGF).[147] Both these angiogenic factors appear to play a role in the formation of neocapillaries to support the hyperplastic intima. VEGF production in the arterial wall is correlated with the concentration of interferon (IFN)-γ in the tissue.[147] IFN-γ is produced by T lymphocytes in the adventitia of the inflamed artery.[148] These T cells undergo clonal expansion in the artery and continue the disease process by regulating macrophages.[149,150] Eradication of these T cells eliminates the disease, but IFN-γ production has been shown to be relatively resistant to standard corticosteroid treatment.[151] Aspirin has been shown to decrease IFN-γ production in the artery.

Arterial medial wall damage is the precursor to intimal hyperplasia. This damage is mediated by oxidative stress in the mitochondria of macrophages. Mitochondrial genes of macrophages have been found to be highly expressed in arteritic lesions.[152] Evidence of reactive oxygen species from macrophages has been detected by antibodies to lipid peroxidation products in damaged smooth muscle membranes. These reactive oxygen intermediates combine with nitrogen intermediates to cause protein nitration of endothelial cells. The exact functional consequences of nitration in medial endothelial cells need to be investigated. With the fragmentation of the internal elastic lamina by metalloproteinases, myofibroblasts can migrate into the intimal layer where they proliferate and deposit extracellular matrix. Expansion of the hyperplastic intima is supported by neocapillaries via angiogenic factors derived from specialized macrophages. Hyperproliferation of the intimal layer may then ultimately lead to stenosis and occlusion (Figure 2.3).[152]

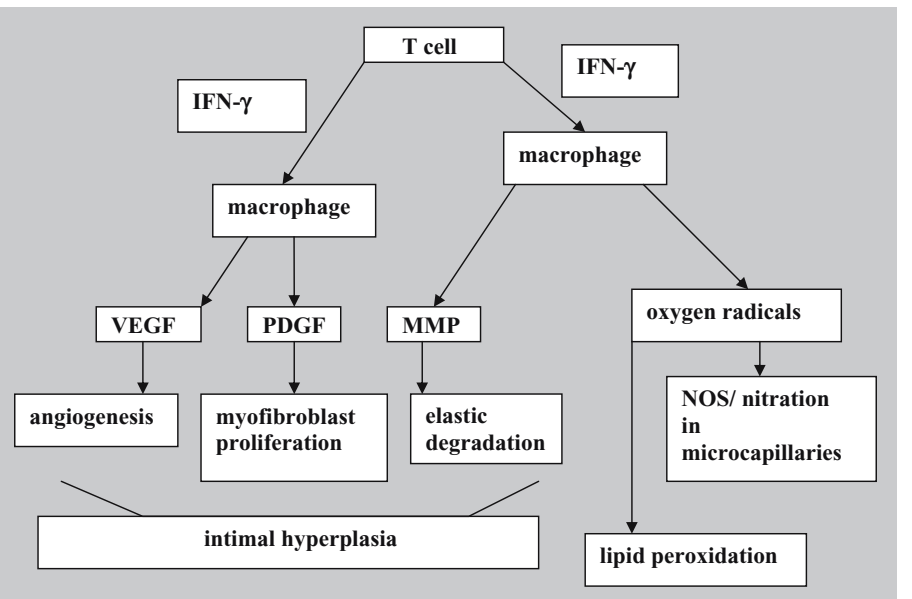

FIGURE 2.3. Mechanisms of vascular injury in GCA. (Adapted from Weyand and Goronzy.[153])

Evidence involving microorganisms as an etiological factor in GCA has been conflicting. Varicella-zoster virus and *Chlamydia pneumoniae* have been shown to be associated with GCA based upon DNA polymerase chain reaction (PCR) analysis.[154,155] Other studies have not supported these data. Haugeberg et al.[156] did not detect *C. pneumoniae* by PCR in any of the 20 histologically proven biopsies of GCA. Regan et al.[157] reevaluated 90 biopsies and found no evidence of the *C. pneumoniae* 16S rRNA gene. In another smaller prospective study by Helweg-Larsen et al.,[158] PCR analysis did not detect *C. pneumoniae*, parvovirus B19, or all the eight human herpes viruses [herpes simplex virus (HHV) 1 and -2, Epstein–Barr, cytomegalovirus, varicella-zoster, and HHV-6, -7, -8].

Diagnosis of GCA

The American College of Rheumatology established clinical criteria for the diagnosis of GCA (Table 2.1).[159] The sensitivity of three of the five criteria is 93.5% and the specificity is 91.2%. These criteria are guidelines and are not absolute, as other connective tissue disorders or malignancies can mimic the clinical presentation of GCA.[160]

An ESR is present in more than 95% of patients with biopsy-proven GCA. The risk of developing GCA is not correlated with the degree of elevation, and 8% to 22% of patients with biopsy-proven GCA have a normal ESR.[161–164] Therefore, patients with symptoms and signs suggestive of GCA with an ESR in the normal range should still undergo a temporal artery biopsy. Because no definitive studies exist on the range of ESR in normal persons, formulas by Miller et al.[165] allow an estimation of the normal ESR. The maximum normal ESR for a man may be calculated by dividing his age by 2. For a woman, the maximum normal ESR is equivalent to her age plus 10 divided by 2.[165] An elevated ESR is not specific for GCA and may occur in other systemic inflammatory diseases. An elevated ESR with an elevated C-reactive protein (CRP) are considered more sensitive in diagnosing GCA in 97% of cases. The CRP is more sensitive at 100% sensitivity than the ESR at 92% sensitivity in patients with GCA.[143] CRP rises more rapidly in the acute phase of GCA and responds more rapidly to the effects of treatment.[143]

Thrombocytosis in which the platelet count is elevated to greater than 400×10^3/L may yield better diagnostic results than the ESR in terms of positive predictive value and negative predictive value in patients suspected of having GCA.[166] In a retrospective study of 91 patients who underwent temporal artery biopsy, the positive predictive value was 87% and the negative predictive value was 67% when using the platelet count as a diagnostic test for GCA. Using the ESR for diagnosis resulted in a positive predictive value of 54% and a negative predictive value of 55%.[166] Because corticosteroids have been shown to cause an approximate 25% reduction in the mean platelet count, this may serve as a marker of response to treatment.[167] Another retrospective comparison of 121 biopsy-confirmed GCA patients with 287 patients with NAION did not confirm these findings.[168] Patients with GCA had significantly higher platelet counts, ESR, CRP, and WBC, but lower hemoglobin and hematocrit values compared to the NAION group. The predictive ability of elevated platelet count as a diagnostic marker for GCA was similar to that of ESR or CRP.

Although the pretreatment ESR may be a prognostic indicator for duration of treatment, CRP and interleukin-6 (IL-6) may be more sen-

TABLE 2.1. Diagnostic criteria for GCA by the American College of Rheumatology, 1990[159]

The American College of Rheumatology 1990 criteria for the diagnosis of giant cell arteritis include three or more of the following:

- More than 50 years of age at disease onset
- New onset of localized headache
- Temporal artery tenderness or decreased temporal artery pulse
- Elevated ESR (Westergren) greater than 50 mm/h
- Biopsy sample including an artery showing necrotizing arteritis characterized by predominance of mononuclear cell infiltrates or a granulomatous process with multinucleated giant cells

sitive indicators of disease activity than ESR in GCA patients.[169]

The temporal artery biopsy is the gold standard for diagnosis of GCA. A positive result can support continued therapy despite some of the risks of corticosteroid adverse effects. Temporal artery biopsy should be performed within 1 to 2 weeks of corticosteroid treatment because of the alteration of arterial inflammatory infiltrates by this medication.[170] Because skip lesions may lead to false-negative biopsy results in 4% to 5% of cases, it is recommended to obtain a biopsy specimen on the clinically affected side measuring at least 3 cm long.[171] If a unilateral temporal artery biopsy is negative, a contralateral biopsy may increase the yield of capturing a positive result by 8% to 13% in patients with typical symptoms and signs of GCA.[172] With a negative unilateral temporal artery biopsy, several studies have suggested a poor yield of a second biopsy when clinical suspicion for GCA is low.[173] In fact, a retrospective study revealed that only 1 of 88 patients with a unilateral negative biopsy had a subsequent positive contralateral temporal artery biopsy.[172]

Because of differing biopsy results for each artery in a bilateral biopsy, which may range from 3% to 13%, some experts prefer to routinely perform bilateral biopsies.[172,174,175] Whether it is done unilaterally or bilaterally, the temporal artery biopsy should be done whether or not the patient has started corticosteroids. In a prospective study of patients with a clinical diagnosis of GCA, 86% (six of seven) of patients who underwent a temporal artery biopsy after 4 weeks of corticosteroid treatment still had cellular infiltrates characteristic of active GCA.[176] Disruption or loss of the internal elastic lamina may be present up to 6 months after initiation of steroids.[170] If clinical suspicion of GCA is high in a patient with a negative biopsy, a second biopsy should be done.[145,172] If a patient with negative bilateral biopsies is strongly suspected of having GCA, this patient should be treated despite negative biopsy results.

The pathological diagnosis of GCA requires the presence of macrophages in the elastica, with or without multinucleated giant cells. A lymphocytic infiltrate is often seen in the intimal and medial layers, in addition to the adventitia.[177] The presence of lymphocytes may result from surgical manipulation during the biopsy or to vasculitis other than GCA. Inflammatory changes may not be continuous along the artery and may result in skip lesions in approximately 8% of cases.[178] Chronic arteritis may show intimal thickening, fibrosis, vascularization, fragmentation of the elastic lamina, and some lymphocytes.[179] Besides the presence of macrophages in the elastica, another important pathological feature is the reduplication, interruption, and fragmentation of the internal elastic lamina.[180] The identification of internal elastic membrane calcification is diagnostically important because the inflammatory process in GCA starts as a foreign-body giant cell attack on calcified parts of the internal elastic membrane.[181]

Color Doppler imaging of orbital and ocular blood flow is not used routinely and has not replaced temporal artery biopsy.[182] Although it can image the course of the affected superficial temporal artery, seen as a hypoechoic halo effect from edema of the arterial wall,[183,184] the procedure is operator- and equipment dependent and is not capable of distinguishing inflammatory from atheromatous lesions. The sensitivity of a hypoechoic halo was 40% and its specificity was 79% for the diagnosis of GCA confirmed by temporal artery biopsy.[185]

Extensive choroidal hypoperfusion seen on fluorescein angiography is helpful in the diagnosis of GCA. Arteritic AION affects both the posterior ciliary and choroidal vessels compared to NAION, which affects only the posterior ciliary circulation.[145] In patients with AION, there is a delay of choroidal filling by more than 15 or 18 s. This delay of choroidal filling associated with acute visual loss and normal optic discs is suggestive of PION caused by GCA.[145]

Magnetic resonance imaging (MRI) has a limited role in the diagnosis of patients with GCA. It may be used to investigate other etiologies of visual loss, especially when patients present with atypical symptoms. MRI findings can reveal enhancement of the orbital fat and optic nerve. Optic nerve sheath enhancement represents fibroadipose tissue containing arteries with intimal thickening and mild mural

inflammation consisting predominately of lymphocytes and occasional giant cells.[186] Multifocal dural and temporalis muscle enhancement, and perivascular enhancement of the superficial temporal artery, have also been reported in patients with GCA.[187]

Magnetic resonance angiography (MRA) or cerebral angiography in GCA may demonstrate irregular narrowing or stenosis of the superficial temporal artery.[188–190] MRA may be useful when bilateral temporal artery biopsies are normal in a patient highly suspected of having GCA.[191]

Treatment of GCA

Corticosteroids are the only proven effective therapy for stopping visual loss in patients with GCA. High-dose corticosteroid with methylprednisolone at 1 g/day IV for 3 to 5 days followed by high-dose oral prednisone is considered the treatment of choice to prevent further damage of the affected eye and to prevent visual loss in the fellow eye. Dosage in the range of 1 mg/kg/day to 2 mg/kg/day should be given if oral prednisone alone is used. This therapy should be maintained for about 4 weeks until symptoms subside and serum markers of inflammation normalize. Early high-dose oral or intravenous corticosteroids for at least 2 weeks has been shown to be effective in preventing further visual loss in most patients with GCA.[192] Prednisone can then be slowly tapered over the next 12 to 18 months with monitoring of the ESR and CRP. Prednisone can be decreased by 10 mg each month, and then more slowly by 5 mg or 1 mg each month when a dose of 10 or 15 mg is attained. If GCA is highly suspected, steroids should not be delayed until biopsy confirmation has been obtained. The artery remains abnormal for at least 2 weeks after steroids are started.[170] If the patient has a positive temporal artery biopsy, higher doses of corticosteroids should be used during the first 2 months when the risk of new ocular ischemia is highest. A definitive, biopsy-proven diagnosis requires at least 6 months, and usually 12 months, of corticosteroids.

Only 4% to 15% of patients with arteritic AION experience improvement in visual acuity, but not in visual fields, with treatment.[193,194] Despite high-dose steroids, progression of visual loss or second-eye involvement can occasionally occur within 5 days of initiation of treatment.[195]

After the first 4 weeks of treatment when steroids are tapered, more than 50% of patients have recurrence of symptoms and elevation of the ESR and CRP as an indication of disease activity that requires an increase of prednisone to the previous dose before relapse.[192] Recurrence of arteritic AION in the same affected eye is rare and may occur without systemic symptoms or elevation of ESR and CRP.[195] In the series by Hayreh and Zimmerman,[193] no patients on high-dose prednisone experienced blindness after the first 5 days. However, a higher rate of late visual impairment was noticed during tapering of prednisone with a shift to alternate-day treatment after 3 months.

Although GCA has been considered a self-limiting disease after 1 to 2 years of treatment,[196] studies have demonstrated that GCA can have a protracted course with multiple relapses.[197,198] In two studies,[197,198] the mean duration of steroid therapy was 5.8 years with a range from 0 to 12.8 years. After 5 years, 43% of patients were still on therapy, and after 9 years 25% continued on treatment. Despite adequate control of symptoms by corticosteroids, underlying inflammation may still persist in patients with GCA. Although corticosteroids effectively inhibit nuclear factor-κB pathways to suppress cytokines, such as IL-1, IL-6, and IL-2, contributing to systemic symptoms, interferon-γ production is unaffected and it continues to help maintain the inflammatory infiltrate in the vessel wall. In a retrospective review of 100 patients with biopsy-proven GCA,[199] 10% of patients had ipsilateral recurrence of AION from 3 to 36 months after the initial AION. Although 83% of patients had elevated acute-phase reactants or new systemic symptoms consistent with GCA, only 17% developed these clinical premonitory features with enough lead time to allow physicians to prevent recurrence of visual loss.

Because of the complications of long-term corticosteroids, such as osteoporosis, steroid-

sparing agents can help reduce the maintenance dose of prednisone. Evidence supporting the use of these various agents is limited or inconclusive. Four small prospective and retrospective series describe the use of two immunosuppressive agents in 16 patients with corticosteroid-resistant GCA and 1 patient with corticosteroid-resistant polymyalgia rheumatica.[200–203] Among the patients in these various studies, the add-on agent to corticosteroids was cyclophosphamide, dapsone, or methotrexate. Information regarding diagnostic criteria and measures of disease activity was limited in these small studies. Methotrexate was shown in some studies to be effective as an adjunctive treatment in GCA.[204–206] Some patients were able to reduce their corticosteroid maintenance dose by using supplementary methotrexate. Studies on the combined effect of methotrexate and corticosteroids yielded conflicting results.[204,205] In a randomized, controlled, double-blind study by Spiera et al.,[206] 21 patients with GCA were treated with either high-dose corticosteroids and methotrexate starting at 7.5 mg/week or placebo. Corticosteroids were tapered according to the clinical response, with methotrexate or placebo dose increased by 2.5 mg/week for relapses with a maximum allowable dose of 20 mg/week. After clinical remission and discontinuation of prednisone, methotrexate or placebo was tapered monthly to 0 by 2.5 mg/week. No significant difference was seen between the methotrexate- and placebo-treated patients with regard to the cumulative corticosteroid dose, the number of weeks to completion of steroids, the number of weeks to taper prednisone to less than 10 mg/day, and the bone mineral density in the lumbar spine or hip at 1 year. No late visual loss occurred in either group. Therefore, this study clearly shows that treatment with methotrexate and corticosteroids is a safe alternative to corticosteroid therapy alone in patients with GCA and is more effective in controlling disease. Jover et al.[205] also reported that the combination of methotrexate and corticosteroids was more effective than prednisone alone in maintaining disease remission, and that the cumulative mean dose of corticosteroids was lower in the methotrexate group after 2 years. However, these findings were not confirmed in a larger multicenter 1-year study by Hoffman et al.,[204] which showed that the addition of methotrexate to a conventional steroid regimen did not improve disease control or reduce steroid dose. The disparity of the foregoing study results could be attributed to differences in study size, inclusion criteria, criteria for determining relapse, and dosage in tapering protocols. To what extent these differences in treatment regimen might have contributed to the different results is not known.

Azathioprine has been shown to be an effective adjunctive treatment in GCA. In a randomized, double-blinded, placebo-controlled study,[207] 9 of 16 patients (5 with biopsy-proven GCA) who received azathioprine at an average dose of 1.5 mg/kg/day to 2.7 mg/kg/day completed the 52 weeks of therapy; other patients did not because of medication-related adverse effects. A statistically significant lower mean dose of prednisone was noted in the azathioprine group compared to placebo.

Cyclosporin A was shown in an open, controlled, randomized study to have no additive effect compared with prednisone alone in GCA.[208]

For patients who have corticosteroid-resistant GCA, tumor necrosis factor blockers have been shown in some case reports to be effective. The inflammatory infiltrate in GCA consists of mostly T lymphocytes, macrophages, and giant cells. Cytokines, such as tumor necrosis factor-α, are released by activated macrophages and T cells. Although increased serum levels of tumor necrosis factor-α have not been demonstrated in patients with GCA, up to 60% of cells in GCA inflammatory lesions have tumor necrosis factor-α.[209] Tumor necrosis factor-α microsatellite polymorphisms have also been associated with GCA.[209,210]

Because tumor-necrosis factor-α is one of the major cytokines mediating inflammation in GCA, agents that block this factor have been used in some patients with treatment-resistant GCA. Infliximab is an antitumor necrosis factor-α monoclonal antibody used successfully in six patients with GCA who were resistant and/or intolerant to corticosteroids and methotrexate.[211] In a study of four patients who had corticosteroid-related side effects while on this

medication from 42 to 54 months and recurrent relapses while tapering to 7.5 to 12.5 mg/day,[209] they received two infusions of infliximab at 3 mg/kg. Three patients had clinical remission with discontinuation of corticosteroids after 5 to 6 months. Infliximab was well tolerated without any major side effects.

Uthman et al.[212] administered a larger dose of infliximab at 5 mg/kg that was used as monotherapy to successfully control GCA in a 75-year-old woman after her initial course of prednisone. Another tumor necrosis factor blocker is etanercept, which has been used in the treatment of corticosteroid-resistant GCA. In a report by Tan et al.,[213] an 80-year-old man with GCA who had been treated with more than 20 mg/day prednisolone was started on etanercept 25 mg po BID. Within 1 month, his symptoms improved. His prednisolone was then reduced to 5 mg/day and his etanercept was decreased to once every 8 days. Etanercept has also been used in treatment-resistant cases of GCA.[209,210]

Acetylsalicylic acid (ASA) may have an anti-inflammatory action in patients with GCA. In a study of a mouse chimera model of GCA,[214] ASA predominantly suppresses transcription of interferon-γ. It may be able to inhibit T-cell function and prevent progression of intimal hyperplasia and luminal occlusion. Because ASA can also inhibit platelet aggregation, it has been postulated that it may be used with other anticoagulants, such as clopidogrel, for thrombosis. Thrombosis has been documented in vertebral arteries affected by GCA,[215] but an occlusive vasculopathy from intimal proliferation also causes ischemia in GCA. Among the 175 GCA patients in a retrospective study by Nesher et al.,[216] patients receiving low-dose aspirin were five times less likely to experience cranial ischemic complications (AION and strokes) by the time of diagnosis. Low-dose aspirin users were also fivefold less likely to develop cranial ischemic complications after prednisone was started. Low-dose aspirin decreased the absolute risk of cranial ischemic complications after GCA was diagnosed from 13% to 3%. This study suggests that low-dose aspirin significantly reduces the rate of AION and strokes in patients with GCA, despite that the aspirin-treated group had more risk factors for cardiovascular disease.

Visual Prognosis of AION in GCA

Despite treatment, worsening of vision may continue. Recovery of vision is rare and only occurs in less than 15% of patients.[217]

Based on a retrospective study of 114 eyes of biopsy-proven GCA patients who were treated with high-dose corticosteroids, 4% (5 of 114) of eyes with initial visual loss had improvement in visual field and visual acuity of greater than two lines.[217] Ninety-one percent had AION, 10.5% had central retinal artery occlusion, 10% had cilioretinal artery occlusion, and 4% had posterior ischemic optic neuropathy. Seven eyes from 6 patients had improvement in visual acuity without improvement in visual fields. Eccentric fixation could have accounted for previously higher reported rates of visual recovery after treatment in past clinical studies.

In another study of 32 patients with biopsy-proven GCA treated with high-dose corticosteroids,[194] 13% (5 of 39) of eyes with initial visual loss from AION had improvement in visual acuity of more than two lines. However, these patients had continued impairment from their severe peripheral constriction. The visual prognosis of AION from GCA is generally poor.

A high proportion of patients with permanent visual loss have been shown to have had delayed diagnosis and treatment. In a retrospective review of 146 patients by Font et al.,[218] 35% of patients had systemic symptoms for an average of 10 months before visual loss and 65% noted premonitory visual symptoms for an average of 8.5 days. Other studies[219,220] also showed a clear relationship between visual improvement and the time to diagnosis and initiation of treatment. If treatment was started within 24 h from onset of symptoms, visual improvement was noted in 58% of patients, compared with only 6% in those who had a longer delay in treatment. Early initiation of treatment appears to be the most important factor in successful treatment of visual complications from GCA, because 92% of the visual losses often occur before the start of therapy.[221]

Other Etiologies of Arteritic AION

Although the most common vasculitic disorder causing arteritic AION is giant cell arteritis, other etiologies include herpes zoster, relapsing polychondritis, polyarteritis nodosa,[222] rheumatoid arthritis, Wegener's vasculitis,[223,224] Takayasu's arteritis, Behçet's disease, Crohn's disease, and connective tissue disorders such as systemic lupus erythematosus, periarteritis nodosa, and Churg–Strauss angiitis.[225] Rarely, infections, such as *Rickettsia conorii*, can be present with AION.[226]

Posterior Ischemic Optic Neuropathy

Incidence of PION

Arteritic and nonarteritic conditions may affect the retrobulbar portion of the optic nerve to cause posterior ischemic optic neuropathy (PION), which is much less common than AION. In a retrospective study of 72 patients with PION,[227] 38 of 72 had nonarteritic PION, 6 of 72 had arteritic PION, and 28 of 72 had perioperative PION. Patients with nonarteritic PION had similar vasculopathic risk factors as those with NAION, but they did not have a small cup-to-disc ratio. Patients with arteritic PION were older and had more severe visual loss with less recovery; those with perioperative PION were younger and had bilateral visual loss with poor recovery.

Symptoms and Signs of PION

In PION, visual loss is acute and painless, associated with a relative afferent pupillary defect, and a central visual field defect, alone or in combination with other types of field defects. The optic disc in PION usually appears normal, in contrast to disc edema seen in AION. Within 4 to 6 weeks, the optic disc usually becomes pale. Progressive PION may occasionally lead to gradual visual loss over week to months. PION is a diagnosis of exclusion (Table 2.2).[228]

TABLE 2.2. Diagnostic criteria for PION (adapted from Buono et al.[228])

- Acute visual acuity loss and/or visual field defect with decreased or absent color defect.
- Ipsilateral relative afferent pupillary defect (RAPD) in unilateral involvement or minimally reactive or nonreactive pupils in bilateral involvement.
- Normal optic disc and retinal examination at the onset of visual loss.
- Exclusion of other identifiable causes of visual loss, such as retinal vascular occlusion, glaucoma, anterior segment trauma, etc.
- Exclusion of other causes of retrobulbar optic neuropathy, such as compression, demyelination, vasculitis, etc.
- Abnormal visual evoked potential.
- Normal electroretinogram.
- Development of optic disc atrophy or pallor within 4 to 8 weeks of onset of visual loss.

Pathophysiology of PION

The posterior optic nerve is supplied only by the pial capillary plexus from the ophthalmic artery and is separate from the vascular territory of the anterior optic disc which is supplied by the paraoptic branches of the short posterior ciliary arteries. The pial capillary plexus is relatively poorly vascularized. More posteriorly, the intracanalicular optic nerve is supplied by two independent vascular circles derived from the ophthalmic artery. The intracranial portion of the optic nerve is also supplied by a separate vascular system from branches of the ipsilateral internal carotid, anterior cerebral, and anterior communicating arteries.[19]

PION in Systemic Disorders

Retrobulbar optic nerve ischemia has been shown to be related to cardiovascular and cerebrovascular diseases. Carotid artery disease may cause PION as an isolated event or as part of the optico-cerebral syndrome in which a hemispheric stroke is associated with an ipsilateral PION.[19] Optic atrophy may develop in the affected eye within 2 months of onset of visual loss. Severe carotid atherosclerosis may also cause NAION in one eye and progressive PION in the fellow eye. Chronic ischemia from

ipsilateral carotid occlusive disease can lead to a slowly progressive PION that may be complicated by iris neovascularization.[229] PION is also more commonly a complication of spontaneous rather than traumatic carotid artery dissection.[230]

PION can occur in the clinical setting where a fistula may steal blood away from the intraorbital optic nerve. A posterior-draining dural carotid cavernous sinus fistula fed by the right meningohypophyseal trunk and right middle meningeal artery and an ophthalmic-middle meningeal arterial anastomosis led to the development of a right PION in a 79-year-old woman who presented with acute right visual loss, ocular motor abnormalities, and pulsatile tinnitus.[231]

Other inflammatory diseases that can cause PION include giant cell arteritis, lupus, polyarteritis nodosa, and herpes zoster. Inflammation of the medial posterior ciliary artery from herpes zoster ophthalmicus, causing acute visual loss with a deep, steep-sided altitudinal visual field defect, has been associated with PION.[232]

Infections have been associated with PION. Fungal embolization by *Aspergillus fumigatus* to the retrobulbar optic nerve caused acute monocular visual loss in a 35-year-old woman.[233] Herpes zoster ophthalmicus caused inflammation of the medial posterior ciliary artery that led to PION, in addition to retinitis, iris sphincter damage, and corneal scarring.[232]

Although AION has been well described in patients after an episode of classical migraine (migraine with visual aura), PION has been reported in two patients with PION.[234] PION can occur as acute visual loss during or after a migraine, or following an episode of visual aura without headache.

An acute isolated PION has been reported as the presenting sign of a ruptured anterior communicating artery aneurysm.[235] Because the ischemic optic neuropathy usually occurs ipsilateral to the subarachnoid hemorrhage, it is hypothesized that the hemorrhage caused a decreased blood supply to the posterior circulation of the optic nerve. In a report by Hara et al.,[236] two patients developed disc atrophy with excavation and permanent superior altitudinal defects after the subarachnoid hemorrhage.

PION often is a complication of arachnoiditis affecting the intracranial optic nerves and chiasm in basal meningitis, head injury, intracranial tumor, empty sella syndrome, foreign-body reaction to muslin wrapping, or systemic disease. Ischemia is induced by compression of the optic nerve from vascular occlusion and fibrosis in arachnoiditis. PION is also presumed to occur in lymphoma, sepsis, intranasal corticosteroid injection, intranasal epinephrine-containing anesthetic injection, and amyloidosis.[19]

PION has been reported in sickle cell disease in a 52-year-old black man with a history of sickle cell with SS trait.[237]

Perioperative PION

Hypotension from anemia or from any decrease in blood flow to the ipsilateral common or internal carotid artery during surgery may cause PION.[228] Most cases of perioperative PION occur with acute blood loss after procedures, such as radical neck dissections, cardiopulmonary bypass, lumbar spine, and major abdominal surgeries. The incidence of perioperative PION is estimated to range from 0% to 0.12% according to several case series.[238–243] Of 14,102 cases of spine surgery at the Johns Hopkins Hospital over 20 years, the incidence of PION was 0.028% (4 cases). More than 50% of patients with perioperative PION develop visual loss after lower spine surgery after being in the prone position for a prolonged period of time. More than 70% develop bilateral PION.[244]

Most affected patients are in their fifth decade and experience acute visual loss in the postoperative period, less than or equal to 24 h after recovery from anesthesia. Visual acuity may range from 20/70 to no light perception (NLP). According to a review of the literature by Buono et al.,[228] approximately 61% of patients had bilateral simultaneous visual loss and none had sequential involvement; those with bilateral visual loss experienced the worst visual deficits.[228] About 38% of patients had some visual recovery, but about 86% with NLP initially had no visual improvement. Those with better vision initially had more substantial visual recovery. Overall, about half of all eyes

had a final visual outcome of hand motion or worse. All patients developed optic disc atrophy. Approximately 66% of patients had vascular risk factors, such as hypertension, diabetes mellitus, hypercholesterolemia, coronary artery disease, congestive heart failure, cardiac arrhythmia, obesity, and tobacco use. The remainder had no vascular risk factors. The average duration of operation was 8.7 h. The mean decrease of hematocrit was 14.4% between the preoperative and the perioperative period. The mean decrease of systolic blood pressure was 53 mmHg between the preoperative and the perioperative period. The mean intraoperative estimated blood loss was 3.7 L.

If no intraoperative hypotension is documented during the surgery, then anemia is most likely, as evidenced by a mean hemoglobin level that has decreased by 40% to 50% in the perioperative period.[228]

Neuroimaging of the optic nerves in the perioperative setting can sometimes show the location of the lesion in PION. In a report of a 61-year-old man with bilateral PION after cardiac bypass surgery, MRI of the orbits with diffusion-weighted and fluid-attenuated inversion recovery (FLAIR) sequences can reveal abnormal hyperintensity in both intraorbital optic nerves.[245] Bilateral intraorbital optic nerve enhancement was seen on MRI 8 weeks after coronary bypass grafting in a 57-year-old woman who had hypotensive posterior ischemic optic neuropathy.[246]

Histopathology demonstrates that infarction occurs in the intraorbital portion of the optic nerve in patients with perioperative PION. The central axial portion of the optic nerve is usually infarcted, and may be hemorrhagic, with sparing of the nerve periphery. Occasionally, the infarction may extend to the periphery circumferentially, especially in the midorbital section of the optic nerve. The loss of peripheral axons appears to correspond to constricted visual fields.[247–249] In the report by Nawa et al.[248] on a 67-year-old man with bilateral PION after radical neck dissection complicated by intraoperative hypotension and anemia, histopathology of the optic nerve revealed acellularity of the fibrovascular pial septae, swollen macrophages, some hemorrhage, and loss of myelin. The paracentral pial vessels had a few small thrombi, but no emboli.

Perioperative hemodynamic changes causing decreased oxygen delivery to the optic nerve are thought to cause PION. These hemodynamic factors include hypotension, anemia, increased venous pressure, a prone position during surgery, direct ocular compression, increased cerebrospinal fluid pressure, and embolism. Another factor that may decrease oxygen delivery to the optic nerve is defective vascular autoregulation caused by vascular endothelial dysfunction.[250] It has been shown that normal compensatory vasoconstriction and vasodilation during fluctuating blood pressures does not occur in diabetic patients.[251] This lack of vascular autoregulation during perioperative hypotensive episodes would increase the risk of developing perioperative PION. Anatomic variation of the intraorbital blood supply may also account for a patient's susceptibility to perioperative PION. The arterial supply of the intraorbital optic nerve derives from two separate systems, the peripheral centripetal vessels and the axial centrifugal vessels.[252] The pial plexus is formed by collaterals directly from the ophthalmic artery and from collateral from other intraorbital subdivisions of the ophthalmic artery. The axial system is formed from branches of the central retinal artery after it penetrates the optic nerve sheath. These branches radiate from the central optic nerve to penetrate the parenchyma. The anastomoses between the peripheral and central vascular systems may vary among patients. Those who lack these anastomoses have a watershed zone that is more susceptible to ischemia during perioperative hemodynamic changes.[252]

Treatment for PION is limited at this time. Perioperative correction of hemodynamic abnormalities may be beneficial in certain instances. In a report by Stevens et al.,[242] correction of anemia and hypotension led to complete visual recovery in one patient, who received blood transfusions to maintain a hematocrit above 35% and a blood pressure about 140/80 mmHg by discontinuation of antihypertensive medications. Postoperative visual acuity was 20/70 in the right eye (OD) and 20/200 in the left eye (OS). After transfusion, visual acuity

was 20/40 OD and 20/30 OS. Seven months later, his visual acuity improved to 20/20 OU. This report suggests that early transfusion for perioperative anemia can prevent perioperative PION. Specific clinical guidelines for transfusion have been controversial, and the decision to transfuse should be based upon the patient's risk of developing complications of decreased oxygenation.[253]

In addition, simultaneous internal jugular vein ligation should be avoided to prevent PION after radical neck dissection. Staging of the neck dissection does not appear to prevent PION.[254–257]

PION as a Complication of Ocular or Sinus Surgery

See "Traumatic Optic Neuropathy."

PION as a Complication of Radiotherapy

See "Nutritional and Toxic Optic Neuropathies."

Treatment of PION

The visual prognosis for PION is usually poor. No proven effective treatment is available to reverse visual loss.[19]

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3
Papilledema

Jane W. Chan

Papilledema is clinically defined as optic disc swelling resulting only from increased intracranial pressure (ICP), as opposed to the optic disc swelling from other etiologies, such as ischemia or inflammation (Table 3.1). Cerebrospinal fluid pressure (CSF) equal to or greater than 250 mmH_2O taken in a person lying in the lateral recumbent position is considered abnormally elevated. Normal CSF pressure is usually in the range of 100 mmH_2O to 250 mmH_2O.[1]

Symptoms of Papilledema

One of the most common symptoms of increased ICP is headache.[3] It is usually a dull, pulsatile, occipital or generalized headache. It can occur daily and last for hours. The headache is not related to the ICP changes or other associated symptoms. It may be worsened with Valsalva maneuvers, such as coughing or straining. It is usually associated with neck stiffness, nausea, and vomiting. Occasionally, retrobulbar pain may occur with eye movement. Pain may even radiate to facial dermatomes.[3]

Transient visual obscurations may involve blurry vision to complete loss of vision and are thought to be related to transient ischemia of the optic nerve.[4] Acute episodes of blurry vision are the most common and usually last less than 30 s and rarely several hours.[5] They may be monocular or binocular and are not related to the degree of intracranial pressure or to the severity of papilledema. These visual symptoms are precipitated by postural changes.[5] Positive visual phenomena, such as photopsias and phosphenes, are also transient and are thought to be related to traction of the retrobulbar optic nerve or retina.[6]

Pulsatile tinnitus is often unilateral and is eliminated temporarily by compression of the ispilateral jugular vein and by lowering CSF pressure by a lumbar puncture (LP). High-pressure vascular pulsations are thought to be transmitted by CSF to the venous sinus walls to cause this tinnitus.[6]

Signs of Papilledema

The key feature of increased ICP is papilledema and may be classified into the following four different stages: (1) early, (2) fully developed, (3) chronic, and (4) atrophic.[7]

A very early sign of papilledema is hyperemia, dilatation of capillaries on the disc surface. The retinal nerve fiber layer also loses its superficial curvilinear light reflexes to become more red. The optic disc usually is swollen, initially in the inferior pole, then at the superior pole, followed by the temporal and nasal aspects, respectively (Figure 3.1).[8] Because of the disc swelling, the optic disc margins become blurred. Rupture of a distended capillary within or surrounding the disc may also cause peripapillary nerve fiber layer hemorrhages. These flame-shaped hemorrhages appear as thin streaks of blood on or near the margins of the optic disc. Because of the elevated intracranial pressure, spontaneous retinal venous pulsations are absent. CSF

TABLE 3.1. The differential diagnosis of the swollen disc (adapted from Miller and Newman[2])

Not true disc swelling: congenitally anomalous, elevated optic disc

- With and without buried drusen
- Tilted optic disc
- Hypoplastic optic disc

True disc swelling

- Elevated intracranial pressure: secondary to mass lesion, cerebral venous thrombosis, or idiopathic (pseudotumor cerebri)
- Inflammatory: infections, demyelination, sarcoidosis
- Vascular: anterior ischemic optic neuropathy, central retinal vein occlusion
- Compressive: secondary to neoplasms (meningioma) or thyroid ophthalmopathy
- Infiltrative: secondary to neoplasms (leukemia) or sarcoidosis
- Toxic/metabolic/nutritional deficiency
- Hereditary: Leber's hereditary optic neuropathy
- Traumatic optic neuropathy

pressures of 200 mmH_2O or greater may even inhibit these pulsations. As 20% of persons with normal CSF pressure have spontaneous venous pulsations, the observation of spontaneous venous pulsations only indicates that the CSF pressure is below 200 mmH_2O at that time and is not always a reliable sign of papilledema.[7]

In more fully developed papilledema, peripheral retinal veins become engorged and dark. Closer to the disc, splinter hemorrhages may be seen as edema in the retinal nerve fiber layer increases at or adjacent to the disc margin. More flame-shaped hemorrhages may appear as a result of sudden rises of CSF pressure. The surface of the disc then becomes elevated above the retinal surface, and microaneurysms and dilated capillaries appear. The peripapillary surface blood vessels become obscured by more edema in the retinal nerve fiber layer. Focal retinal infarcts, or cotton wool spots and tortuous vessels, appear (Figure 3.2).[7,8]

In severely elevated ICP, circumferential choroidal folds, or Paton's lines, may develop. Choroidal folds may even be the initial presenting sign of increased ICP, according to a study by Griebel and Kosmorsky.[9] Ten of 12 patients had ICPs of greater than 120 mmH_2O, and 8 of 12 were diagnosed with idiopathic intracranial hypertension (IIH). Four patients had increased ICP and choroidal folds in the absence of papilledema. It was hypothesized that the choroidal folds might represent enlargement of the retrolaminar optic nerve sheath in the absence of axonal swelling. Alternatively, it was proposed that the choroidal folds might persist after resolution of papilledema. The presence of choroidal folds in isolation might be related to the timing of the evaluation.

Hard exudates and hemorrhages may occur in the peripapillary region and in the macula to cause decreased central vision. Development of macular edema may be a risk factor for permanent visual loss in IIH. In a study by Talks et al.,[10] 44% (21 of 48) of eyes in 24 patients who had progressive visual deterioration from IIH requiring optic nerve sheath fenestration developed macular changes, including choroidal folds, Paton's lines, nerve fiber layer hemorrhages, subretinal hemorrhages, macular

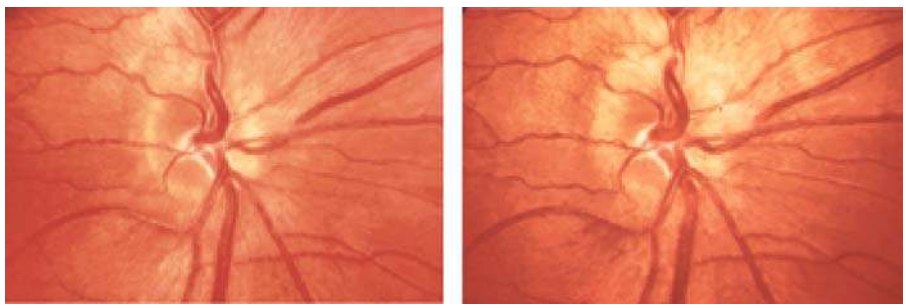

FIGURE 3.1. Early stages of papilledema. Early nerve fiber layer edema is first seen superiorly (*left*), then inferiorly and nasally (*right*). (Reprinted from Spalton et al.,[8] with permission from Elsevier.)

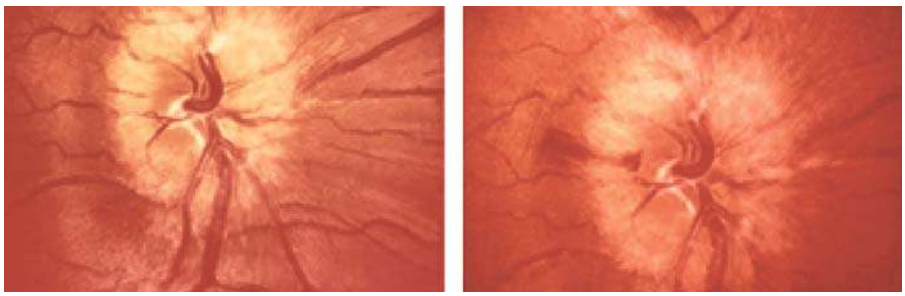

FIGURE 3.2. Later stages of papilledema. Venous engorgement increases as further disc swelling extends temporally (*left*). Hemorrhages and cotton wool spots also develop (*right*). (Reprinted from Spalton et al.,[8] with permission from Elsevier.)

stars, macular edema, and retinal pigment epithelial changes. These changes probably contributed to the severe visual loss in 5 eyes, 3 of which did not improve despite treatment. It was concluded that these macular changes might not have had a significant impact on optic nerve-related visual loss in patients with IIH, but the patients who developed macular edema might be at greater risk for permanent visual loss.

If ICP increases abruptly, severe subhyaloid hemorrhages may occur and occasionally bleed and dissect into the vitreous in about 4% of patients with papilledema.[11] These intraretinal hemorrhages are often the result of compression of the central retinal vein from the swollen optic disc and usually resolve with treatment of elevated ICP.[12]

In chronic papilledema, hemorrhages and exudates slowly resolve, and the optic disc cup is gradually destroyed (Figure 3.3).[8] The disc may have hard exudates mimicking disc drusen, a sign that the papilledema has been present for several months. Nerve fiber layer atrophy may also appear as slitlike defects on red-free direct ophthalmoscopy.[13] Chronic papilledema may even persist for many years without significant visual symptoms, especially in patients with pseudotumor cerebri or with intracranial tumors.[14]

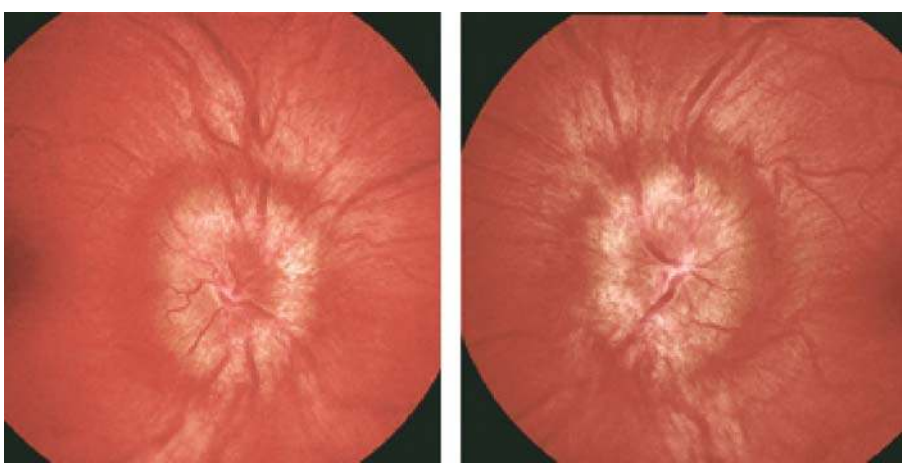

FIGURE 3.3. Chronic papilledema. Both optic discs (*left and right*) are swollen with no hemorrhages or cotton wool spots, indicative of a slow, gradual increase in cerebrospinal fluid (CSF) pressure. (Reprinted from Spalton et al.,[8] with permission from Elsevier.)

If left untreated, chronic papilledema will result in disc pallor with attenuated and sheathed retinal vessels.[15,16] The nerve fiber layer appears dull, and some patients have persistent pigmentary changes or choroidal folds in the maculae.[16,17]

The duration for each of the stages of papilledema just described varies among individuals. Not all patients with papilledema progress through these stages. Some may begin with fully developed papilledema and then advance to the chronic stage, followed by the atrophic stage when optociliary shunt vessels appear.[18–20] These preexisting veins shunt blood from the retinal to the choroidal venous circulation.[21] The elevated ICP is believed to compress the central retinal vein directly or the optic nerve indirectly to cause these vessels to become enlarged and thereby visible. The optic atrophy resulting from chronic papilledema also causes a selective loss of peripheral axons with sparing of central axons so that central visual acuity is spared.[22]

Asymmetric papilledema, when one eye appears to have more severe papilledema than the other, may occur in the Foster Kennedy syndrome.[23–26] Frontal lobe or olfactory groove tumors compress the ipsilateral optic nerve to cause optic atrophy. Meanwhile, growth of the mass causes increased intracranial pressure, which then distends the contralateral optic nerve sheath, resulting in papilledema. Previous lesions in the optic chiasm or optic tract can also lead to asymmetric papilledema.[23–26] Patients with temporal hemianopia and atrophy of nasal fibers have band atrophy with sparing of the most upper and lower (temporal) arcuate fibers. During papilledema, the swelling is limited to the superior and inferior regions of the disc. In patients with nasal hemianopia, atrophy of temporal fibers and swelling is limited to the nasal region of the disc.[27]

Unilateral papilledema in normal optic discs occur in approximately 4% of cases. It is thought to be secondary to varying degrees of communication between the subarachnoid space and optic nerve head through the optic canal.[28] In a report by Krishna et al.,[29] a young obese woman presented with headache and a left sixth nerve palsy without optic disc swelling. Her CSF was normal except for an opening pressure of 440 mmH_2O. Magnetic resonance imaging (MRI) of the brain was normal, and her symptoms resolved completely on acetazolamide treatment. Atrophic or anomalous discs may not develop papilledema, except in regions of the disc where some axons are still functioning. Therefore, most cases of unilateral papilledema represent bilateral asymmetric papilledema.

Central vision is affected in papilledema. Visual acuity may range from normal to no light perception (NLP). The visual acuity is not related to the degree of papilledema, except for atrophic papilledema in which the vision would be invariably poor. However, contrast sensitivity defects do correlate to the severity of visual loss. Acute loss of central vision is usually a late phenomenon that can be related to local ischemia, such as ischemic optic neuropathy or retinal vascular occlusions related to a rapid rate of increase in ICP or to an underlying coagulopathy.[30,31] Along with loss of visual acuity, visual field defects develop slowly and progressively. Concentric enlargement of the blind spot is the most common defect, followed by isopter constriction, and loss of the inferior nasal quadrant of the visual field with a nasal step.[32] Color defects usually involve red-green abnormalities. No afferent papillary defect is detected in most instances of papilledema (bilateral). One-third of patients have horizontal diplopia. One-fifth of these are sixth nerve palsies; the remainder have third nerve palsies, fourth nerve palsies, or hypertropias.[16]

Diagnostic Testing

Although papilledema is most often diagnosed by careful ophthalmoscopic examination, some cases of optic disc swelling may not be so apparent. Fluorescein angiography may diagnose early papilledema in only some instances.[33,34] An A- and B-scan ultrasound with a 30° test when indicated can help determine whether the optic disc is truly swollen and if there is increased ICP.[35] A computed tomography (CT) scan of the orbits can delineate calcium deposits to distinguish the drusen from papilledema. To evaluate for an intracranial mass or

hydrocephalus, CT or MRI of the brain with and without contrast should be done. A lumbar puncture can then be performed to measure the ICP.[7]

Pathology

On histopathology, the optic nerve head with papilledema protrudes into the vitreous, displaces the adjacent retina, and causes folds in the posterior retinal layers. The compression and displacement of the peripapillary retina are thought to contribute to the enlargement of the blind spot.[36,37] Peripapillary subretinal fluid can cause hyperopia from elevation of the retina and can also lead to a refractive scotoma, or enlarged blind spot.[38]

The prelaminar portion of the optic nerve is swollen whereas the postlaminar aspect is not. The papilledema arises from intraaxonal swelling.[39] Increased numbers of mitochondria, disorganized neurofilaments, and accumulation of intracellular membranes also can be seen. Necroses appear from prolonged ischemic of the compressive effects of the angulated nerve fibers exiting the optic nerve head.[40,41]

Possible Mechanisms of Visual Loss Related to Papilledema

Histological evidence and the types of visual field defects seen in IIH localize the site of the lesion at the optic nerve head. Increased ICP is translated along the subarachnoid space of the optic nerve sheath, which causes an increased pressure gradient across the optic nerve head. This pressure within the optic nerve contributes to axoplasmic stasis. According to Tso et al.,[42] both slow and fast axoplasmic transport is disrupted, resulting in intraaxonal edema. Another potential mechanism of visual loss in IIH is optic disc ischemia. Delays in prelaminar arterial filling are seen on fluorescein angiography in patients with papilledema. The visual field defects occurring in patients with papilledema are also similar to those found in other ischemic optic neuropathies, such as glaucoma and anterior ischemic optic neuropathy. The axoplasmic stasis, intraaxonal edema, and compression of small arterioles lead to optic nerve ischemia.[44]

Major Causes of Increased Intracranial Pressure

Intracranial masses, such as abscesses, arteriovenous malformations, hemorrhages, infarctions, inflammatory masses, and neoplasms, may cause increased ICP by displacement of space in the cranium, produce focal or diffuse cerebral edema, or obstruct CSF flow by blocking CSF drainage. CSF obstruction may be by direct compression of venous sinuses or indirectly by the production of protein that obstruct infiltration through the arachnoid villi by such tumors as carcinomas, lymphomas, leukemias, and leptomeningeal gliomatosis. Infratentorial tumors more often than supratentorial ones cause papilledema. Infratentorial tumors often obstruct the aqueduct or compress the vein of Galen or superior sagittal sinus. Supratentorial tumors usually compress the falx or vein of Galen. Other types of supratentorial tumors located in one of the lateral ventricles or in the nondominant hemisphere may also cause papilledema without any localizing signs. Only 60% of intracranial tumors cause enough increased intracranial pressure to result in papilledema. Other mass lesions include hematomas and abscesses.[44]

Aqueductal stenosis is associated with papilledema. The stenosis may be congenital and may or may not be associated with a Chiari malformation. Infants present with macrocephaly, whereas adults present with papilledema, headache, dorsal midbrain syndrome, meningitis, hemorrhage, pituitary compression causing endocrinological dysfunction, seizures, gait ataxia, and CSF rhinorrhea.[7]

Among congenital conditions, mucopolysaccharidosis is a common cause of ICP and papilledema. Deposition of mucopolysaccharides in the arachnoid villi inhibits resorption of CSF.[7] Craniosynostosis may also cause decreased venous outflow through the jugular foramina.

Approximately 15% of patients with premature synostosis of the cranial sutures develop papilledema, whereas other types, such as oxycephaly, scaphocephaly, and trigonocephaly, often do not. Papilledema develops in about 40% of patients with craniofacial dysostosis, such as Crouzon's syndrome and Apert syndrome. Papilledema, if it develops, usually presents before the age of 10 years.[45]

By blocking CSF flow in the ventricles or by obstructing CSF absorption into the arachnoid villi, subarachnoid hemorrhage may also cause increased ICP and papilledema. Ten percent to 24% of patients with ruptured intracranial aneurysms develop papilledema within several hours or weeks.[46]

By causing diffuse cerebral edema, obstructing the aqueduct, and/or obstructing CSF resorption in the arachnoid villi, meningitis and encephalitis may produce increased ICP and papilledema.[47] About 2.5% of patients with meningitis develop papilledema.[48] Tuberculous meningitis is the most common cause, followed by cryptococcal meningitis in which the papilledema may be more severe. Papilledema usually resolves with treatment of the infection.

Granulomatous infections, such as syphilis, tuberculosis, and sarcoidosis, may cause nodular masses and fibrosis of the meninges that obstruct CSF flow.[7] About 20% of patients with viral encephalitis, especially herpes simplex and herpes zoster, have papilledema.[49] California encephalitis, lymphocytic choriomeningitis, infectious mononucleosis, Coxsackie meningoencephalitis, and poliomyelitis may occasionally present with papilledema.[50]

Increased CSF protein produced by spinal cord tumors may obstruct CSF resorption in the arachnoid villi. Spinal cord tumors may grow in the cervical region to compress the cerebellum upward and obstruct CSF flow through the foramen magnum, but more often neurinomas and ependymomas in the thoracic and lumbar regions produce these high amounts of protein or blood products from recurrent hemorrhaging, respectively.[7] Paragangliomas in the lower spinal cord may also lead to IIH. In a report by Haslbeck et al.,[51] a patient with a cauda equina paraganglioma presented with papilledema and a right sixth nerve palsy. CT and MRI of the brain were normal. The CSF opening pressure was 330 mmH_2O with increased erythrocytes of 35,000 cells/mm^3 and elevated CSF protein of 4,500 mg/dL. Although these findings were initially attributed to a traumatic tap, a subsequent spinal MRI revealed a paraganglioma extending from L3 to the filum terminale.

By a similar mechanism, elevated CSF protein in Guillain–Barré syndrome and chronic inflammatory demyelinating polyneuropathy (CIDP) may also lead to papilledema.[7] However, papilledema has been observed in patients with CIDP with only mildly elevated CSF protein.[52]

Decreased venous drainage is another common cause of communicating hydrocephalus that may lead to papilledema. The superior sagittal and transverse venous sinuses are most commonly affected. Extraaxial tumors, such as meningiomas, may directly compress the superior sagittal sinus. Acoustic neuromas and metastatic tumors may also compress the transverse sinus. Early papilledema develops in otitis media when complicated by septic thrombosis of the transverse sinus, in which the infection spreads to the mastoid air cells and then to the adjacent lateral sinus. In contrast, papilledema develops late in the course of septic thrombosis of the cavernous sinus. Iatrogenic etiologies, including ligation or occlusion of a jugular vein during surgery or thrombosis of an indwelling catheter, may cause severe papilledema to develop within 2 weeks. It often gradually resolves as collateral veins form to shunt the CSF.[7]

Cerebral Venous Sinus Thrombosis

Cerebral venous sinus thrombosis affects women between 20 and 35 years of age. Young women, those during pregnancy, and especially those during puerperium are at highest risk of developing cerebral venous thrombosis.[53] The superior sagittal sinus is involved in 72% of patients and the lateral sinuses in about 70% of patients. More than one sinus is affected in greater than 30% of patients. In 30% to 40% of patients, both sinuses and cerebral or cerebellar veins are involved. The slow growth of the thrombus and extensive collateralization of the

venous system account for the gradual onset of symptoms over weeks to months.[54] The ischemia from the thrombus causes hemorrhagic infarction in the cortex and adjacent white matter in 10% to 50% of patients.[55–57] Patients with cerebral venous thrombosis can present with headache, papilledema, focal neurological deficits, seizures, and mental status changes.[58] The clinical presentation of cerebral venous thrombosis can vary, but four main types have been identified: (1) focal neurological deficits or partial seizures (75%); (2) isolated increased ICP with headache, papilledema, and sixth nerve palsy (18% to 38%); (3) subacute diffuse encephalopathy without any localizing neurological signs to suggest increased ICP; and (4) acute painful ophthalmoplegia with chemosis and proptosis from cavernous sinus thrombosis.[59,60] In 80% of patients with cerebral venous thrombosis, a cause or predisposing factor can be identified.[60] There is a wide spectrum of etiologies, such as infection, autoimmune disorders, coagulopathies, and tumors (Table 3.2).[61]

Cerebral venous thrombosis has a good long-term prognosis. Up to 86% of patients have complete recovery.[62,63] Mortality ranges from 5.5% to 18%.[59,62] The frequency of long-standing epilepsy was low, suggesting that anticonvulsants do not need to be continued in most patients. Only 12% of patients have a recurrence of cerebral venous thrombosis and 14% have a different type of venous thrombosis.[63]

On CT scan of the brain, the "empty delta sign," representing the opacification of collateral veins in the wall of the superior sagittal sinus after contrast injection, is seen only in 10% to 20% of patients. CT scan of the brain is normal in 10% to 20% of patients with proven cerebral venous sinus thrombosis.[53] The most reliable diagnostic modality for cerebral venous sinus thrombosis is MRI and MR venogram of the brain, which can show thrombosis, cerebral edema, infarction, hemorrhage, and anatomy of the abnormal venous circulation. If the diagnosis is still doubtful, then cerebral angiography may be necessary.[53,56,57] Absence or hypoplasia of the anterior aspect of the superior sagittal sinus, which is a normal variant, can simulate thrombosis on MR venogram. Contrast enhancement may also be mistaken for normal contrast material accumulating within the sinus.[57] Compared to MR venogram, CT venography may better visualize sinuses or cortical veins with low flow.[64]

CSF abnormalities occur in up to 84% of patients and include increased ICP, increased protein, presence of red blood cells, and pleocytosis.[55] Meningitis and subarachnoid hemorrhage must be ruled out before the diagnosis of cerebral venous sinus thrombosis can be established. Acquired and inherited coagulation disorders, such as Factor V Leiden mutation if resistance to activated protein C is abnormal, should be evaluated. Activity of protein C and S, antithrombin III, and levels of plasminogen, fibrinogen, and anticardiolipin antibodies should also be performed before starting anticoagulation and 6 months afterwards.[65]

Anticoagulants as the treatment of choice for cerebral sinus thrombosis have been controversial. In a Cochrane Database Systematic Review,[66] two small trials addressing this issue were selected for analysis. Each trial was an unconfounded, randomized, controlled trial in

TABLE 3.2. Some causes and predisposing factors of cerebral venous sinus thrombosis (adapted from Allroggen and Abbott[61])

- Infection from penetrating head injury, intracranial infection, localized infection elsewhere in the body, and sepsis or systemic infection
- Head injury complication
- Neurosurgery complication
- Stroke and hemorrhage
- Space-occupying lesion
- Infusions from central venous line
- Cardiac disease
- Hormonal and endocrinological causes
- Malignancies
- Red blood cell disorders
- Thrombocytopenia
- Coagulation disorders
- Severe dehydration
- Inflammatory bowel disease
- Connective tissue disorders
- Behçet's disease
- Sarcoidosis
- Nephrotic syndrome
- Drugs (such as L-asparaginase)

which anticoagulant therapy was compared with placebo or open control in patients with cerebral venous sinus thrombosis confirmed by MR angiography or intraarterial contrast. The efficacy of intravenous, adjusted-dose unfractionated heparin was examined in one trial of 20 patients. The efficacy of high-dose, body weight-adjusted, subcutaneous, low molecular weight heparin (Nadroparin) was examined in the other study of 59 patients. The pooled relative risk of death associated with anticoagulant therapy was 0.33 [95% confidence interval (CI), 0.08–1.21] and that of dependency was 0.46 (95% CI, 0.16–1.31). No new symptomatic intracerebral hemorrhages were observed. One gastrointestinal hemorrhage occurred after anticoagulant treatment. Therefore, anticoagulant treatment for cerebral venous sinus thrombosis seemed safe. It did not reduce the risk of death or dependency, but statistical significance was not attained.

Heparin is started as a continuous intravenous infusion at 1000 U/h and is adjusted according to the activated partial thromboplastin time, 1.5 to 2 times control. It is contraindicated in patients who are actively bleeding or who have hypersensitivity to the drug. Some side effects include hemorrhage and hypersensitivity reactions. Immune-mediated thrombocytopenia occurs in 2% to 5% of patients receiving unfractionated heparin. Oral warfarin is usually started after a few days and adjusted to obtain an International Normalized Ratio between 2 and 3. Warfarin may be continued up to 3 months, based upon a study by Einhaupl and Masuhr[67]; no recurrence of cerebral venous thrombosis occurred after 3 months of anticoagulant treatment. However, warfarin may need to be continued so long as the risk of cerebral venous thrombosis is present, as in patients with malignancy, inflammatory disease, inherited thrombophilia, etc.

In women who have had a history of cerebral venous thrombosis during pregnancy or a history of recurrent deep venous thrombosis, low molecular weight heparin is usually given for preventative treatment. For women who have postpartum cerebral venous thrombosis, low molecular weight heparin is continued after delivery for up to 1 month for prophylaxis.

Although intravenous and intrasinus thrombolysis have been used in patients who fail heparin, intrasinus infusion with streptokinase or urokinase is faster than the intravenous route. Delivery of the thrombolytic agent, such as tissue plasminogen activator (tPA) or urokinase, locally to the clot requires a lower dose associated with less risk of hemorrhage. Local endovascular urokinase or tPA can also be used in patients with brain edema and hemorrhage.[61] More randomized, controlled data are needed to clarify the details of delivery techniques, choice of drugs, drug dosages, etc.

Idiopathic Intracranial Hypertension

The most common symptoms of IIH, or pseudotumor cerebri, include headache, transient visual obscurations, pulsatile tinnitus, and diplopia.[3] In a prospective study of 50 IIH patients who were mostly obese women, 94% had headache, 68% had transient visual obscurations, 58% had tinnitus, 26% had visual loss, 54% had photopsias, 38% had diplopia, and 44% had retrobulbar pain.[68] In a review of 82 patients,[69] 68% of patients had specific headache disorders, such as episodic tension headache in 30% and migraine without aura in 20%. These patients with IIH often had headaches unrelated to increased ICP, and these headaches often persist despite normalization of the ICP.

The presentation and course of IIH in older affected patients is slightly different. In a study of 9 women and 5 men,[70] 64% were obese, 36% were asymptomatic, and none presented with headache alone. Twenty-nine percent had secondary causes of increased ICP, including transverse sinus thrombosis, chronic obstructive pulmonary disease and cor pulmonale, and corticosteroid withdrawal after prolonged administration. After 2 years of follow-up, 12 patients remained in the study. Eight had stable visual fields, 3 had improved visual fields, and 1 had worsened field defects. It was concluded that more patients over 44 years of age were more often men, were less often obese, were less symptomatic, and had identifiable causes of

elevated ICP in 29%. The visual prognosis in this age group appeared to be good.

Papilledema may be absent in some cases of IIH, especially in obese women and some men with new daily persistent headache (NDPH) syndrome,[71] the acute onset of headache within 3 days that is persistent for 15 days or more each month for at least 3 months.[72] Conversely, IIH can be present with papilledema and normal CSF opening pressure.[74] (Please see Symptoms and Signs of Papilledema in earlier sections of this chapter.)

Diagnostic Criteria

The accepted criteria for the diagnosis of pseudotumor cerebri have been the modified Dandy criteria put forth in 1985, which include symptoms of ICP, no localizing neurological signs, except for false ones, normal brain imaging results, an awake and alert patient, ICP greater than 250 mmH_2O, normal CSF findings, and no identifiable cause of increased ICP.[73]

Updated diagnostic criteria for IIH have been proposed by Friedman and Jacobson,[1] which include the following. (1) If symptoms are present, they may only reflect those of generalized intracranial hypertension or papilledema. (2) If signs are present, they may only reflect those of generalized intracranial hypertension or papilledema. (3) Elevated intracranial pressure must be measured in the lateral decubitus position. (4) CSF composition must be normal. (5) There should be no evidence of hydrocephalus, mass, or structural or vascular lesion on MRI or contrast-enhanced CT for typical patients and no such abnormalities on MRI and MR venography for atypical patients. For these atypical patients with suspected IIH, the incidence of venous sinus thrombosis and other vascular anomalies simulating IIH is sufficiently high that MRI and MR venography are recommended. MRI and MR venography should also be considered for adults and children with a recent history of sinus infection or otitis media, those who present with rapid visual loss, or patients who do not respond to conventional treatment. (6) There should be no other cause of intracranial hypertension identified (Table 3.3).[70,75,76]

TABLE 3.3. Updated diagnostic criteria for IIH (as proposed by Friedman and Jacobsen[1])

Updated diagnostic criteria for IIH as of 2002 include the following:

- If symptoms are present, they may only reflect those of generalized intracranial hypertension or papilledema.
- If signs are present, they may only reflect those of generalized intracranial hypertension or papilledema.
- Elevated ICP must be measured in the lateral decubitus position.
- CSF composition must be normal.

There should be no evidence of hydrocephalus, mass, structural, or vascular lesion on MRI or contrast-enhanced CT for typical patients, and no such abnormalities on MRI and MR venography for atypical patients.

Epidemiology/Genetics

Pseudotumor cerebri usually affects obese teenage girls and young child-bearing women. The prevalence is about 1 case per 100,000 women. For women between the ages of 20 and 44 years who are 20% above ideal body weight, the prevalence is higher, at 19 cases per 100,000 women.[77] The average age of onset ranges from 11 to 58 years, with a mean of about 30 years.[77–80]

Men are affected less frequently. The prevalence is 0.3 cases per 100,000 men, but in men who are more than 20% above their ideal body weight, it increases to 1.5 cases per 100,000 men. The ratio of male to female is approximately 1 : 4.3 to 1 : 8.[73]

This disorder is rarely familial, and it has not been confirmed by genetic studies whether it is autosomal dominant.[1]

Visual Course and Prognosis

The most significant complication of pseudotumor cerebri is blindness or permanent visual impairment from chronic papilledema resulting in optic atrophy. Because the swelling of the optic disc may appear to decrease because of progressive optic atrophy in chronic papilledema, optic nerve function is the more reliable

parameter to measure. The visual loss is often insidious, and peripheral vision is affected first. Central visual acuity may be affected last in patients with papilledema. In a study of 35 patients with IIH over a 3-year period,[81] visual field assessment was more sensitive than both Snellen visual acuity and Pelli–Robson contrast sensitivity testing. Eighty-seven percent of patients had visual field defects on Goldmann perimetry compared to 82% on Humphrey perimetry. The most common visual field defects were enlarged blind spots, arcuate defects, nasal steps, and peripheral constriction. In a prospective study of 9 patients with IIH and asymmetric papilledema,[82] the eye with greater papilledema tended to have worse visual acuity, contrast sensitivity, and visual field defects. High-grade papilledema might be a risk factor for visual dysfunction. Humphrey automated perimetry and stereophotographs documenting changes in the optic discs over time are most useful in monitoring visual course.

The prognosis of pseudotumor cerebri is usually good. Some patients may remain asymptomatic for years. In about 10% of patients, it will recur. IIH may be a self-limiting condition that spontaneously remits before significant damage occurs to the optic nerve.[83] About 25% of 57 patients in a study by Corbett et al.[84] experienced blindness or severe visual impairment in one or both eyes. These patients with severe visual loss had persistent elevated CSF opening pressures between 220 mmH_2O and 550 mmH_2O on repeat lumbar puncture. Although visual loss is usually gradual, patients with severe papilledema may rapidly become blind. Vision should be monitored closely in patients with papilledema, decreased visual acuity, and frequent transient obscurations, as they may require surgical intervention.

Obesity appears to be correlated with visual outcome. Recent weight gain is associated with later worsening of visual fields.[85] Morbid obesity (body mass index greater than 40 kg/m^2) is also associated with a worse visual outcome.[86]

Losing weight by diet and exercise is associated with improvement in papilledema, but it is not clear whether this change in funduscopic finding affects ultimate visual outcome.[86–88]

Pathogenesis of IIH

Several theories have been put forth to explain the pathogenesis of pseudotumor cerebri. No clear evidence exists to support Quincke's theory that excess CSF production increases CSF volume in pseudotumor cerebri.[89]

Later theories proposed by Foley and Dandy suggested that increased cerebral blood flow could cause elevated ICP.[83,90] Positron emission tomography of the brain has revealed markedly increased cerebral blood or water volumes but almost no change in cerebral blood flow.[91] Recent brain MRI studies on patients with IIH have demonstrated increased water apparent diffusion coefficients and increased white matter water signals. Convective transependymal flow may cause interstitial brain edema and increased brain water content.[92–95]

A more recent theory suggests that elevated venous pressure could lead to increased resistance to CSF absorption and subsequently increased ICP in pseudotumor cerebri.[96,97] Several studies have shown that increased sagittal sinus pressure leads to decreased CSF absorption because CSF pressure is not high enough to drive bulk flow of CSF across the meninges.[96,98] Elevated dural sinus pressures measured during intracranial venography have been demonstrated in patients with no obvious evidence of dural sinus obstruction.[99] In contrast, more recent studies have suggested that the increased venous pressure in IIH may be caused by the elevated ICP and not the reverse. In a prospective study by Farb et al.,[100] auto-triggered elliptic-centric-ordered three-dimensional gadolinium-enhanced MR venography (ATECO MRV) showed that 27 of 29 patients with IIH and only 4 of 59 control patients had substantial bilateral sinovenous stenoses. The sensitivity and specificity of ATECO MRV to identify patients with IIH was 93%. It was thought that the idiopathic narrowing of the venous sinuses in patients with IIH probably represented transverse sinus compression from increased ICP. The increased ICP from IIH might have exacerbated the underlying venous sinus abnormality and created a flow-limiting stenosis and resultant pressure gradient. Venous occlusion and elevated venous

pressure may not be the mechanism for IIH. In another postmortem study of 20 transverse sinuses,[101] the presence of a large septum may be one of the causes of venographic cryptic stenosis located at the junction of the middle and lateral third of the transverse sinus. The venographic cryptic stenosis was thought to be one of the etiological factors involved in IIH.

Because of the increased incidence of IIH in females, endocrinological dysfunction has been hypothesized to contribute to the development of this disorder. Obesity may cause increased intraabdominal pressure, leading to increased right heart filling pressure and subsequently increased central venous pressure.[102,103] Evidence supporting this theory shows that weight loss and bariatric surgery[103,104] decrease papilledema and lower CSF pressures. Acute weight gain may be related to relapses of IIH, and obesity-associated sleep apnea may lead to increased ICP.[105–107] In a study by Lampl et al.,[108] significantly higher levels of leptin, a protein secreted by adipose cells that influences regulation of energy balance and body weight, were found in obese patients with IIH. In a prospective study of 65 patients,[109] plasma levels of ghrelin, a hormone that usually increases during overeating and decreases in obesity, did not differ between patients with IIH and obese control patients. Ghrelin levels were similar during fasting and after eating. Therefore, this hormone does not play a role in the maintenance of obesity in patients with IIH.

Disorders and Medications Associated with Elevated Intracranial Pressure

Various systemic diseases have been associated with increased ICP, including systemic lupus erythematosus,[110–112] underlying malignancies,[113] anemia,[114] Addison's disease,[115] hyperthyroidism and hypothyroidism,[116–118] and uremia (Table 3.4).[119–121]

Cerebral venous sinus thrombosis leads to increased venous pressure and higher CSF pressures, with clinical findings of papilledema and headache.[122] It may closely mimic the symptoms and signs of IIH.[123] (Please see previous section on cerebral venous sinus thrombosis.)

Other venous abnormalities that can elevate intracranial venous pressures include dural arteriovenous fistulae[124] and carotid-cavernous fistulae.[125] A retrospective study by Cognard et al.[124] demonstrated that 9 of 13 patients with intracranial dural arteriovenous fistulas presented with symptoms and signs of IIH, including headache, papilledema, visual obscurations, and horizontal diplopia from sixth nerve palsy. It was thought that the arteriovenous fistulas impaired venous outflow. Three of the patients had tonsillar herniation following lumbar puncture or lumbar shunting, and 1 died.

Iatrogenic disruption of venous drainage,[126] radical neck dissection,[127–129] or catheter-induced subclavian vein thrombosis[128,130] have also been associated with elevated intracranial venous and CSF pressures. Venous sinus compression by tumors have also been reported.[131] Another series[132] of 22 obese young women with IIH showed no evidence of cerebral venous thrombosis on MRI and MRV of the brain. It was suggested that MRV be used to evaluate atypical presentations of isolated intracranial hypertension, such as those occurring in nonobese, male, or elderly patients, or when other clinical features suggest the possibility of cerebral venous thrombosis.

Hypercoagulable states that can lead to dural sinus thrombosis or IIH include malignancies,[133] systemic lupus erythematosus,[110–112] protein C and S deficiencies,[134] antithrombin III deficiency, Factor V Leiden mutations,[135,136] anticardiolipin antibodies,[137,138] oral contraceptive use,[139] and pregnancy.[116] IIH appears to be associated with coagulation disorders and polycystic ovarian syndrome. Exogenous estrogens or pregnancy can predispose patients with these underlying disorders to develop IIH.[140] Immediate treatment involves direct endovascular thrombolytic therapy. Long-term treatment for such hypercoagulable states involves heparin and warfarin anticoagulation.[141]

Many systemic disorders and hereditary conditions have been linked to increased ICP. Severe iron deficiency anemia is associated with pseudotumor cerebri. In a series by Biousse et al.,[142] six patients with IIH developed bilateral papilledema associated with peripapillary hemorrhages. Two had retinal cotton wool spot

TABLE 3.4. Systemic disorders and exogenous agents commonly associated with increased intracranial pressure (adapted from Corbett[170])

Endocrine and metabolic dysfunction
- Addison's disease
- Diabetic ketoacidosis
- Hyperthyroidism/hypothyroidism
- Hypoparathyroidism-primary and secondary
- Obesity, recent weight gain
- Orthostatic edema
- OB/GYN-ecclampsia, oral progestational agents, menarche, menopause, pregnancy
- Turner's syndrome

Exogenous agents
- Amiodarone
- Amphotericin
- Carbidopa/Levadopa (Sinemet) (?)
- Chordecone
- Cimetidine
- *cis*-Retinoic acid: all-*trans*-retinoic acid (for acute promyelocytic leukemia)
- Corticosteroids: prolonged therapy or withdrawal of either systemic or topical forms
- Cyclosporine (?)
- Cytosine arabinoside
- Cytarabine
- Danazol
- Doxycycline
- Fluoroquinolone
- Growth hormone: chronic gonadotropin
- Heavy metals: arsenic, lead
- Indomethacin
- Isotretinoin
- Ketoprofen
- Leuprorelin acetate (LH-RH analogue)
- Levonorgestrel implants (Norplant)
- Lithium carbonate
- Minocycline
- Naladixic acid
- Nitrofurantoin
- Oral contraceptives
- Oxfloxacin
- Oxytocin (intranasal) (?)
- Pancreatic enzyme
- Perhexiline maleate
- Phenothiazine
- Phenytoin
- Stanozol
- Sulfonamides
- Tamoxifen
- Testosterone
- Tetracycline
- Vitamin A

Systemic disorders
- Behçet's disease
- Chronic respiratory insufficiency: Pickwickian syndrome, obstructive sleep apnea
- Occult craniosynostosis
- Guillain–Barré syndrome
- Hematological disorders: antiphospholipid antibody syndrome, anemia, idiopathic thrombocytopenic purpura, thrombophilia
- Hypertension
- Infectious disorders: HIV, Lyme disease, psittacosis, syphilis, viral meningitis, subacute bacterial endocarditis, bacterial meningitis
- Multiple sclerosis
- Neoplastic disorders: leukemia, spinal cord tumors, carcinomatous meningitis
- Polyangiitis overlap syndrome
- Polycystic ovarian syndrome
- Renal disease
- Reye's syndrome
- Sarcoidosis
- Sjogren's syndrome
- Systemic lupus erythematosus

and two had preretinal hemorrhages. All had severe iron deficiency anemia. Their symptoms and signs of IIH markedly improved after treatment of the anemia. It was suggested that a complete blood count be checked in patients with IIH, especially without known associated factors, such as obesity or medications, or when therapy to lower ICP does not improve the patient's condition. Although headache in sickle cell disease (SCD) is usually attributable to anemia or cerebrovascular disease, three children, one with SCD-SC and two with SCD-SS, who presented with headache and bilateral papilledema and enlarged blind spots developed IIH.[143]

Sleep apnea is associated with IIH in men. In a study by Lee et al.,[144] 6 of 32 men with IIH had sleep apnea. Of the 6 patients, 1 was treated with acetazolamide alone, 4 received acetazolamide and continuous positive airway pressure (CPAP), and 1 was treated with CPAP alone. All patients had 20/20 or better visual acuity bilaterally, enlarged blind spots, and optic disc swelling bilaterally. Five patients had normal

visual fields after treatment, and 1 patient had residual visual field defects. At the end of follow-up, 3 patients had normal optic discs, 2 had improved papilledema, and 1 had optic disc pallor. Treatment of sleep apnea with CPAP helped improve the symptoms and signs of IIH in affected men.

Other systemic disorders that have been recently linked to increased ICP include primary aldosteronism,[145] hypothyroidism with myxedema, papilledema, and elevated CSF protein,[146] Crohn's disease,[147] Goldenhar's syndrome,[148] and treatment of spontaneous CSF leaks.[149]

Various medications have been associated with increased ICP, including excessive vitamin A,[150] the vitamin A derivatives isotretinoin,[151,152] all-*trans*-retinoic acid,[153–155] tetracycline/minocycline,[156,157] doxycycline,[158] nalidixic acid,[159] fluoroquinolones,[160,161] sulfa drugs,[162] oral contraceptives,[139] progesterone,[163] danazol,[164] corticosteroid withdrawal, especially in children,[165] lithium,[166,167] thyroid replacement therapy after thyroidectomy,[168] and mesalazine[169] (see Table 3.4).[170]

In a study by Jacobson et al.,[171] serum retinol levels in 16 female patients who did not have vitamin A supplementation were significantly higher than in the 70 control patients. It is unclear whether vitamin A metabolism causes increased ICP or if elevated retinol levels represent an epiphenomenon.

In a study of 12 patients,[156] 75% developed increased ICP within 8 weeks of starting minocycline for the treatment of acne. The increased ICP resolved after discontinuing the medication and 3 patients had residual visual loss.

Another study on recombinant human growth hormone (rhGH) showed that 4 of 3332 children developed IIH.[172] Three additional cases of IIH in children receiving rhGH were also reported by Rogers et al.[173] Two of the 3 patients had resolution of papilledema with acetazolamide and with discontinuation of the drug.

Neuroimaging Features of IIH

Findings of brain CT scans have revealed not only slitlike ventricles in 11% of patients with IIH but also enlarged optic nerve sheaths in 47% and empty sella syndrome in 46%.[174] Quantitative analysis of ventricular volume has shown no difference between patients with IIH and age-matched control subjects.[175]

No evidence of ventriculomegaly, mass lesion, or venous sinus thrombosis on CT or MRI is required to establish the diagnosis of IIH. However, some subtle radiologic signs have been associated with IIH. In a study of 20 patients,[176] 80% had flattening of the posterior sclera, 70% had an empty sella, 50% had enhancement of the prelaminar optic nerve, 45% had distension of the perioptic subarachnoid space, 45% had vertical tortuosity of the orbital optic nerve, and 30% had intraocular protrusion of the prelaminar optic nerve. These findings were absent or seen in less than 5% of the 20 control patients. These radiologic signs are not specific for IIH, but their presence supports the diagnosis.

Cerebrospinal Fluid Features

To determine the CSF opening pressure, a lumbar puncture performed on the patient in a relaxed, lateral decubitus position is required for establishment of the diagnosis of pseudotumor cerebri. A CSF opening pressure greater than 250 mmH_2O would fulfill one of the modified Dandy criteria mentioned previously.[73] Forty-two percent of asymptomatic obese female patients have opening pressures of greater than 250 mm H_2O.[177] In some cases, papilledema may be seen in patients with an opening pressure of less than 250 mmH_2O. If the diagnosis is uncertain, ICP monitoring with intraparenchymal pressure monitors may be necessary.[178]

Management of IIH

Patients with papilledema, regardless of the cause of the increased ICP, should be followed at regular intervals to detect the earliest evidence of an optic neuropathy. Central visual loss is usually a late phenomenon. Arcuate scotomas and nasal steps are commonly an early finding. Color defects can occur at any stage. Most visual defects associated with papilledema are reversible if the ICP is lowered before

severe visual loss, chronic papilledema, or optic atrophy develops. Monitoring of the best corrected visual acuity at distance and near, color vision testing, visual field testing with kinetic and automated static perimetry, and ophthalmoscopic examination of the optic disc with fundus photos should be done every 1 to 2 weeks for very unstable patients, or every 1 to 3 months for moderately stable patients, and up to every 4 to 12 months for stable patients.[179]

Medical Treatment

The two major goals of therapy in IIH are to prevent visual loss and treat and prevent headaches. If the patient has mild to moderate (grade 1 to 2) papilledema, normal visual acuity, and visual fields (except for an enlarged blind spot) without headaches, then weight loss and a low-salt diet can be tried. Weight loss may be beneficial for patients with IIH, especially if they are supervised by professional dieticians in weight loss programs.[179] In one retrospective series,[88] obese women with IIH who lost weight (mean weight loss of 13.3 ± SD 9.9 pounds) had decreased papilledema and improved visual fields compared to those who did not lose weight (mean weight loss of 0.2 ± SD 0.6 pounds). In a study of 15 patients by Johnson et al.,[87] a weight loss of 6% was associated with a marked improvement of severe papilledema. Although weight loss was correlated with decreased papilledema, visual acuity and visual field were not.[86,88] Severe obesity with a body mass index of greater than 40 kg/m^2 was associated with a worse visual outcome.[86]

Certain medications, such as vitamin A, vitamin A derivatives, and tetracycline, must be avoided as much as possible, but pediatric patients with IIH receiving all-*trans*-retinoic acid[153–155] as chemotherapy for leukemia should not discontinue their treatment. The secondary IIH syndrome should be treated.

If headaches develop, then antimigraine medications may be added. The chronic headaches of IIH are best treated prophylactically. Because many of these agents, such as tricyclic antidepressants, calcium channel blockers, and sodium valproate, may cause weight gain or edema, newer antiepileptic medications may be considered as better alternatives. Short-term weight gain as a side effect may lead to worsening or recurrence of IIH. Topiramate, an antiepileptic medication with mild carbonic anhydrase inhibition, may prove effective in headache relief and weight loss. Studies on the efficacy of topiramate in decreasing elevated ICP are being studied. For abortive therapy, the triptans and nonsteroidal antiinflammatory agents may be useful.[179]

If the patient develops moderated (grade 3) papilledema with decreased visual acuity and abnormal visual field defects in addition to an enlarged blind spot, acetazolamide 1 g/day may be necessary. To lower the CSF pressure, carbonic anhydrase inhibitors, such as acetazolamide, are the most effective medications, as shown by Rubin et al.,[180] in which 6% to 57% of patients experienced a decrease in CSF production. Carbonic anhydrase inhibitors reduce sodium transport across the choroid plexus epithelium and is believed to decrease production of CSF. Acetazolamide is commonly prescribed at a dose of 500 mg (extended-release) p.o. QD or BID increased until a daily dose of a maximum of 3 g/day is achieved. Contraindications to acetazolamide include sulfonamide allergy, significant hepatic or renal disease, and chronic angle-closure glaucoma.[181] The side effects of this medication include a metallic taste to carbonated beverages, paresthesias, anorexia, metabolic acidosis, drowsiness, and confusion. Renal calculi and aplastic anemia rarely occur.[181] Acetazolamide is continued until symptoms and signs resolve and then it is slowly tapered off. If clinical features of IIH recur during tapering, it is continued indefinitely.[179]

Alternatively, methazolamide, which may be slightly less effective and has a lower incidence of side effects than acetazolamide, may be used. Although less effective than acetazolamide or furosemide, a diuretic with a mild effect on CSF production may also be used in patients who cannot tolerate acetazolamide. For patients who are allergic to sulfa, triamterene and spironolactone may be tried. However, these drugs have no proven effect on CSF production.[179]

Furosemide, a loop diuretic with weak carbonic anhydrase activity, has also been reported

as an alternative to acetazolamide or as combination therapy.[182] Furosemide is started at 20 mg/day to 80 mg/day and may be increased up to 160 mg/day. It is contraindicated in anuric patients. Some side effects include excessive diuresis leading to dehydration and hypotension, hypokalemia, and hyperchloremia.[181]

If the patient has severe (grade 4 or 5) papilledema associated with macular edema, retinal hemorrhages, visual acuity of worse than 20/50, and progressive visual field defects, then acetazolamide may be increased up to 4 g/day. A short course of high-dose corticosteroids can be added for the treatment of acute visual loss from papilledema,[183] especially while arranging surgical intervention. Solumedrol 250 mg IV QID for 5 days, with oral taper at 80 mg over 4 to 8 weeks with acetazolamide at 500 mg p.o. BID is often used. Common side effects from corticosteroids include weight gain, fluid retention, increased intraocular pressure, and hyperglycemia, which are problematic in patients with IIH.[165,183]

Serial lumbar punctures are not recommended, but patients with severe papilledema and sudden visual loss may need immediate lumbar puncture and drainage of a large volume of CSF until surgical intervention can be arranged.[184]

Surgical Treatment

Indications for surgery include the following: (1) progressive visual loss despite maximal medical treatment, (2) severe or sudden visual loss at onset with an afferent pupillary defect or signs of advancing optic nerve dysfunction, and (3) severe papilledema causing macular edema or exudates.[184] The degree of visual worsening despite maximal medical treatment may be defined as the development of loss of greater than 2 lines of Snellen visual acuity, generalized field constriction of greater than 20°, or the development of a new visual field defect.[184]

Optic nerve sheath fenestration (ONSD) has been shown to be safe and effective in treating vision in IIH. Visual acuity is stabilized or improved in 93% to 97% of eyes; visual field is stabilized or improved in 85% to 95% of eyes.[185–187]

ONSD involves cutting a window in the dura and arachnoid of the bulbous portion of the edematous optic nerve sheath. This procedure decreases disc swelling on the operated side, and in some instances the contralateral papilledema also. It is more effective in acute papilledema than in chronic papilledema.[188] The mechanism of ONSD in IIH remains unclear. It may filter out CSF locally to reduce pressure to allow improvement in peripapillary circulation. It may also globally lower ICP and occasionally relieve headaches in one-third of patients undergoing unilateral ONSD.[184,187,189] Lastly, a more likely hypothesis is that postoperative scarring of the arachnoid shifts the pressure gradient posteriorly from the lamina cribrosa to the myelinated portion of the optic nerve[190, 191] to protect the optic nerve head from elevated CSF pressure. Improvement in blood flow to the optic nerve has been shown in color Doppler studies where blood velocities in the ophthalmic, short ciliary, and central retinal arteries increased after ONSD.[17] In a retrospective study[185] of 158 eyes, 94% (in 86 patients) who underwent ONSD had stable or improved visual acuity; 88% had improvement in their visual fields. Only 13% (8 of 61) patients reported improvement in their headaches following ONSD. Repeat ONSD was performed on 9 eyes in 6 patients for progressive visual loss. All 9 eyes had stable or improved visual acuity, and 5 of 8 had stable or improved visual fields. Forty-five percent had benign and transient postoperative complications. The most common complication was diplopia, which spontaneously resolved in 87% of patients. In conclusion, ONSD is recommended when medical treatment, such as diuretics and weight loss, are not effective in preventing further progressive visual loss. Progression in visual loss involves developing a new visual field defect, a generalized constriction of greater than 20°, or a loss of more than 2 lines of Snellen acuity. ONSD may not be the treatment of choice for those who have progressive visual loss and intractable headaches, which is better managed by ventriculoperitoneal (VP) or lumboperitoneal (LP) shunting.

The benefits of ONSD are not long term. It does not consistently reduce ICP and, there-

fore, does not treat the underlying problem of IIH. More than 80% of patients with IIH develop recurrent papilledema within 1 year of the procedure. In a study of 11 ONSDs in 75 eyes of 54 patients with IIH,[192] 32% of ONSDs failed within 39 months after surgery. Only about 75% of ONSDs were functioning 6 months after surgery, and the likelihood of a functioning ONSD steadily decreased thereafter such that 66% of ONSDs were functioning at 12 months, 55% at 3 years, 38% at 5 years, and 16% at 6 years after surgery. Although patients could be treated with a second ONSD after initial failure, eyes that had more than one ONSD rarely stabilized or improved after surgery and were more likely to experience a significant vascular complication than eyes that underwent only one ONSD.[193]

The medial approach to the orbit is preferred, but some surgeons do the lateral approach, which requires an orbitotomy. The advantages of the medial approach include the following: (1) quicker access to the optic nerve; (2) retrobulbar anesthesia may be sufficient; and (3) no skin incision is required. Disadvantages of the medial approach are that (1) the medial rectus must be disinserted; (2) the bulbous portion of the nerve may be difficult to see because of the oblique angle of the approach; (3) the placement of a retractor against the inner surface of the medial rectus muscle may damage its innervation; (4) the potential for papillary dysfunction exists; and (5) adjunctive lateral orbitotomy may still be required to provide better exposure of the optic nerve.[194]

The most common complications of ONSD are diplopia from transient lateral rectus palsy and pupillary dilation resulting from sphincter denervation. Transient or prolonged postoperative visual loss is a rare complication (Table 3.5).[195]

TABLE 3.5. A comparison of the complications of surgical treatment for increased IIH (adapted from Binder et al.[195])

Complications of optic nerve sheath fenestration

- Vascular occlusion: central retinal artery occlusion, branch retinal artery occlusion, choroidal infarction
- Hemorrhage in sheath or orbit
- Traumatic optic neuropathy
- Diplopia
- Pupil dilation
- Anterior segment ischemia
- Compressive optic neuropathy from orbital cyst
- Corneal delle formation
- Infection

Complications of lumboperitoneal shunt

- Obstruction
- Infection
- Low-pressure headaches
- Radiculopathy
- Tonsillar herniation
- Syringomyelia
- Subdural hematoma
- Shunt migration

CSF diversion procedures include LP shunting and VP shunting to lower the ICP in IIH. In a review of 134 patients who underwent shunting for IIH[196] between 1942 and 1979 with a mean follow-up of 11.6 years,[196] 14 patients received shunts. Of the 6 patients who had VP shunts, 4 had resolution of symptoms within 6 months. One patient developed a shunt obstruction that required revision and another had a shunt infection that required removal. Of the 8 patients who had LP shunts, all improved within 1 month. One patient had a shunt infection, and 1 had severe low-pressure symptoms from overshunting. In a follow-up study by Johnston et al.[197] on 36 patients who had shunts for the treatment of IIH, 52% had complications and 48% had shunts that failed. The lowest revision and complication rates were associated with LP shunts. Two more recent studies also support that shunting is a reasonable treatment for IIH. In a study of 27 patients with IIH,[198] over a mean of 47 months after shunting, vision improved or remained the same in 14 patients, and headaches improved in all patients. The only serious complication was shunt failure. Fifty-six percent required shunt revision. The average number of revisions per patient was 2.4, with 1 revision required every 2.6 years. In another study[199] of 30 patients who had LP shunting for IIH with a mean follow-up of 35 months, 71% (10 eyes) improved by at least 2 Snellen chart lines and only 1 eye had a

decrease in vision. Sixty-four percent of eyes with abnormal fields had improvement on Goldmann perimetry. The only complication was frequent shunt obstruction. Twelve patients did not need shunt revision. The other patients had an average of 2.5 revisions per patient, except for the 4 patients who needed 10 or more revisions.

The most common complication associated with LP shunts is obstruction, which may account for up to 65% of all revisions. The second most common is secondary intracranial hypotension caused by excessive drainage of CSF via the LP shunt in 15%. Lumbar radiculopathy accounted for 4.5% of all revisions. Other less common problems include shunt infections, tonsillar herniation, syringomyelia, and catheter migration.[198]

A programmable shunt valve can prevent low-pressure headaches, a complication that is less common in VP shunting than in LP shunting. This low-pressure headache is a consequence of overshunting. The most common symptoms of overshunting are postural headaches, neck pain, vomiting, photophobia, blurred vision, transient visual obscurations, visual field constriction, and sixth nerve palsies.[200] MRI findings of intracranial hypotension include leptomeningeal enhancement, tonsillar herniation, and subdural effusions.[201] Stereotactic surgical techniques have also allowed better outcomes with VP shunts, especially in those who experience repeated LP shunt obstructions. In a study of seven patients who were treated with stereotactic VP shunts for IIH, five of the seven patients experienced resolution of papilledema and six of the seven had resolution of headaches postoperatively.[202]

Despite improvements in the external control of intracranial pressure, paradoxical symptoms may occasionally recur. Worsening visual loss, headaches, dizziness, and other pseudotumor cerebri symptoms may indicate shunt malfunction, but they may also occur with a functioning shunt.[201] After many years of remission of symptoms, patients may develop "shunt dependency," increased intracranial pressure when the shunt is removed or even inserted.[203]

The advantages of LP shunting over ONSD as the initial surgical treatment for IIH, as purported by Binder et al.,[195] include the following. (1) LP shunting does not pose a direct risk to the eye. Optic nerve or retinal vascular complications occur in 2% of cases. (2) ONSD in one eye improves papilledema in both eyes, but the results in the contralateral eye are less pronounced. (3) The rate of shunt obstruction is similar to that of ONSD becoming closed from scarring over a similar period. (4) LP shunting is more effective than ONSD in treating headaches because ONSD mainly produces a local decrease in pressure within the subarachnoid space behind the optic nerve head.[204] LP shunting treats the underlying problem of increased ICP and, therefore, treats both papilledema and headaches. (5) Some patients with IIH have sixth nerve palsy that resolves after LP shunt but does not after ONSD. A sixth nerve palsy may even be a complication of ONSD. (6) Papilledema usually resolves after LP shunting if there is no obstruction, but residual papilledema may persist after ONSD.

ONSD may be appropriate for patients with IIH who refuse, cannot undergo, or do not respond to LP shunting. For patients with severe papilledema caused by an inoperable malignant brain tumor, ONSD may serve as a short-term treatment for visual loss. Both immediate ONSD and LP shunting may even be required in patients with IIH who present with marked papilledema and/or macular edema, decreased central visual acuity, severe visual field defect, and ocular motility deficits.[195]

Because of the high rate of complications and failures following VP or LP shunting, bariatric surgery may be an effective alternative in severely obese patients with IIH. However, it is not the treatment of choice in the setting of acute visual loss because its benefit is not apparent until 1 year later. Dramatic decreases in CSF pressure and papilledema have been achieved with gastric stapling.[103] In the study by Sugerman et al.,[104] 19 of 24 patients who underwent bariatric surgery experienced resolution of headache and pulsatile tinnitus. Their average weight loss was 45 kg and their body mass index decreased to $30 \pm 5\,kg/m^2$. CSF opening pressures were not measured in this series, but a previous study by Sugerman et al.[103] showed that CSF opening pressure decreased from 353

± 35 mmH_2O to 169 ± 12 mmH_2O in 8 patients who underwent similar surgery. The mechanism for lowering increased intracranial pressure is unclear. Complications from a gastric bypass, such as a proximal Roux-en-Y procedure, include wound infections, incisional hernias, and stenosis of the gastrojejunal anastomosis. Vitamin deficiencies and osteoporosis are also possible.

Venous sinus stenting may be considered for refractory cases of IIH associated with venous sinus hypertension. In a report by Higgins et al.,[205] a woman with refractory IIH underwent venography and manometry that showed partial obstruction of both transverse sinuses, with raised pressures proximal to the obstructions. Dilation of one of the sinuses with a stent reduced the pressure gradient, with marked improvement in her symptoms. In a later series by Higgins et al.,[205] 12 patients with refractory IIH underwent venography and manometry showing intracranial venous hypertension proximal to stenoses in the lateral sinuses. After venous sinus stenting, intrasinus pressures were variable reduced. Follow-up measurements of CSF opening pressure confirmed a reduction in intracranial pressure. There was no consistent relationship between venous pressure reductions and symptom relief. Five patients became asymptomatic, 2 improved, and 5 were unchanged. Five of the 12 patients had improved or resolved papilledema. It was suggested that lateral sinus stenting be used as an alternative treatment to neurosurgical intervention in intractable cases. In another study by Ogungbo et al.,[206] a 37-year-old woman with IIH had obstruction of the right transverse sinus with high pressure of 40 mmHg proximal to the obstruction and low pressure of 15 mmHg distally, as seen on MRV and cerebral venography. She was treated by transvenous stenting that resolved her symptoms and bilateral papilledema.

It still remains unproven whether the stenoses are the cause or the result of elevated ICP. (Please see section on pathogenesis of IIH earlier in this chapter.)

Angioplasty or thrombolytic infusion was found to improve the venous sinus obstruction but not the clinical syndrome of IIH.[207]

Increased Intracranial Hypertension During Pregnancy

The incidence of IIH in pregnancy is similar to age-matched nonpregnant controls.[208] Although IIH can develop or worsen during pregnancy, the risk of fetal loss is the same as that of nonpregnant age-matched controls.[208] The diagnostic criteria and method of diagnosis is the same as that for the general population. IIH appears to present during the first two trimesters of pregnancy with typical symptoms and signs. Visual outcome is similar to age-matched nonpregnant women.[209] The pregnant patient with IIH is managed in a similar manner to the nonpregnant one with some exceptions. Dieting is not as strict, such that weight gain up to less than 20 pounds is acceptable. Acetazolamide is a category C medication in pregnancy (risk cannot be ruled out because data are lacking), but most neuro-ophthalmologists have been prescribing this medication after the first trimester without known teratogenic effects. Acetazolamide use is recommended after 20 weeks of gestation. Until then, corticosteroids may be administered for visual loss.[182] Corticosteroid use has not been associated with birth defects in humans. Thiazide diuretics are not recommended in the second half of pregnancy. ONSD may be the preferred surgical treatment for progressive visual loss because the enlarging uterus may cause peritoneal catheter obstruction in a shunt.[210] Furthermore, cerebral venous thrombosis should always be considered as the etiology of ICP after delivery or after fetal loss.[211]

IIH in Children

IIH occurs with equal frequency in boys and girls before puberty.[212–214] Adolescent girls are more often affected than adolescent boys.[212] Secondary causes of IIH, such as otitis media, viral infection, medications, and closed head injury, are more commonly seen in about 50% of cases.[215] Antibiotics used in the treatment of these infections may also play a role. Neck

stiffness or torticollis, strabismus, lateral rectus palsy, and facial palsy occur more often in children than adults.[76,216–218] Irritability, apathy, somnolence, dizziness, and ataxia are other presenting signs of IIH in children.[211,219] Headache is less common in children compared to adults. Children with IIH may even be asymptomatic.[219] In a retrospective study of 27 children with IIH with a mean age of 10.9 years, the prepubertal male-to-female ratio was 8:5 and the pubertal male-to-female ratio was 5:9. Obesity was present in 16 (59%) of children. Visual outcome was good except for one who remained symptomatic. IIH did not occur mostly in females in the prepubertal group and was not associated with obesity.

The management of IIH otherwise is similar to that in adults.[182,213]

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4
Compressive and Infiltrative Optic Neuropathies

Jane W. Chan

Compressive Optic Neuropathies

Compression of the Anterior Visual Pathway (Optic Nerve and Chiasm) from Intrinsic Optic Nerve Tumors

Optic Nerve Sheath Meningiomas

Epidemiology

In contrast to the meningiomas from intracranial extension or the ectopic orbital ones, primary optic nerve sheath meningiomas (ONSM) arise from the intraorbital optic nerve sheath and grow circumferentially around the optic nerve to result in an optic neuropathy by interfering with axonal transport and pial blood supply to the nerve. They constitute 1% to 2% of all meningiomas and account for one-third of all primary optic nerve tumors. They are also the second most common optic nerve tumor after glioma.[1] Only 10% of ONSM arise from the orbit, compared to 90% from intracranial extension. More than 90% of ONSM develop in the orbital optic nerve rather than in the canalicular portion.[2]

The mean age of presentation is 40.8 years, according to data from 256 patients.[3] These ONSMs are usually unilateral and occur more frequently among females in a 1:2 male-to-female ratio. Bilateral and multifocal ONSMs occurred in younger patients with neurofibromatosis type II (NF-2),[4] who presented at a mean age of 12.8 years,[2] compared to intracranial meningiomas, which occur around 50 years of age.

Symptoms and Signs

The most common presenting symptom of ONSM is a gradual decrease in visual acuity, which may progress to being moderate or severe, with 15% to 50% of patients having better than 20/40 vision.[5] Transient visual obscurations may also be the presenting symptom, which may be gaze evoked, postural, or spontaneous.[6] Visual field defects often include peripheral constriction, central, centrocecal, and paracentral scotomas, altitudinal defects, and enlarged blind spots.[5,7] Generalized constriction appears to be more frequently seen in patients with canalicular tumors.[8] Proptosis is often mild to moderate and is seen less frequently in patients with canalicular lesions, because they often present with visual loss when the tumor is quite small. Extraocular motility restriction is greatest in attempted upgaze.[9] Approximately half of affected patients have orbital pain and generalized headache.[5]

On funduscopic examination, the optic disc is usually either atrophic or swollen.[6–8] Patients with more posterior or intracanalicular ONSMs who present with slower progressive visual

loss without proptosis or disc edema, however, may present with normal optic discs. As optic nerve compression progresses, the degree of optic atrophy increases.[7,10,11] Optociliary vessels shunting blood from the retinal to choroidal circulation are seen in 15% to 33% of patients and are associated with optic disc edema or atrophy.[6–8] When the compressed optic nerve obstructs flow in the central retinal vein, vestigial retinociliary anastomoses from earlier embryonic development reestablish the flow of retinal venous blood to vortex veins.[12] These optociliary shunt vessels are seldom seen, and they usually appear years after symptoms begin and may involute as optic atrophy is fully developed. These vessels are useful in the diagnosis of ONSMs but are not pathognomonic.[6–8]

Neuroimaging Features

Neuroimaging commonly shows diffuse, tubular enlargement of the optic nerve. This appearance may be confused with optic gliomas, but kinking of the optic nerve (a classic neuroimaging sign of optic gliomas) is not seen in ONSMs. On computed tomography (CT) scan, calcification along the length of the optic nerve may be seen in 20% to 50% of patients, and is sometimes referred to as a "tram-track sign."[7,13] On magnetic resonance imaging (MRI) of the orbits, the tumor is isointense with brain on T_1- and T_2-weighted images and enhances homogeneously with gadolinium. T_1-weighted fat suppression images with gadolinium help delineate the tumor surface adjacent to the orbital fat. This technique demonstrates the tram-tracking sign by enhancing the contrast between the tumor and perineural subarachnoid space.[14]

Other processes mimicking the appearance of ONSMs on neuroimaging include idiopathic orbital inflammatory syndrome (sclerosing type), perioptic neuritis,[15] sarcoid infiltration or other inflammatory infiltration of the optic nerve,[16] metastases to the optic nerve,[17] malignant optic nerve glioma of adulthood, optic nerve glioma in childhood, orbital schwannoma, cavernous hemangioma, lymphangioma, hemangiopericytoma, and optic nerve hemangioblastoma.[18,19]

Histopathology

ONSMs arise from meningothelial cells located uniformly as arachnoid villi along the canalicular and intraorbital regions of the optic nerves. ONSMs are believed to arise from the meningothelial "cap cells" of these arachnoid villi.

Three histological types are seen in ONSMs. In the meningothelial pattern, polygonal cells are arranged in sheets separated by vascular trabeculae. The cells have marginated chromatin and pseudoinclusions, which are invaginated cell and nuclear membranes. Mitoses are uncommon. In the fibroblastic pattern, spindle-shaped cells in parallel configuration are interlaced with bundles of intercellular collagen and reticulin. In the transitional pattern, a mixture of features of the previous two histological types is seen. Spindle or oval cells are arranged in a concentric whorl formation. Psammoma bodies are more commonly seen in this type than in the meningothelial pattern. These bodies develop from hyalinization and deposition of calcium salts in the degenerated central whorls. The calcium formed in these areas accounts for the "tram-track sign."[20]

ONSMs extend along subarachnoid spaces and are encapsulated by intact arachnoid and dura. They commonly invade the optic nerve along its septae, around the spaces surrounding the central retinal vessels,[21] and even through the dura and into surrounding orbital tissues.[14,22] If ONSMs are adjacent to bone, the tumor can extend into the haversian canal system to cause hyperostosis and bone proliferation.[23] ONSMs can also extend posteriorly through the optic canal to the middle cranial fossa but often do not invade the brain.[24] In contrast to meningiomas of the optic chiasm, ONSMs rarely extend into the optic chiasm to the contralateral optic nerve.[2]

ONSMs are often indolent for many months to years, and pregnancy may accelerate their growth so they become clinically apparent.[22] The tumor grows within the subarachnoid spaced to encase the optic nerve. This compression results in impairment of axonal transport, disc edema, optociliary shunt vessels, and eventually demyelination.[25] Continued

compression of the pial blood supply leads to optic atrophy.

Prognosis and Treatment

ONSMs are benign tumors that are slow growing over a period of many years. They typically remain unilateral and rarely extend intracranially. Monocular visual loss, rather than morbidity and mortality, is the primary concern. Many patients maintain good vision for up to 18 years. The mortality rate is very low.[26,27]

Observation is recommended when the ONSM is confined to the orbit and when visual function is good. Serial visual acuity, visual fields, pupillary exam, and color vision testing should be done every 4 to 6 months initially. If the tumor is stable, visual function testing should then be done every 12 months. MRI can be performed once a year. In a retrospective review of 42 patients with unilateral ONSM followed over a mean of 6.2 years,[26] 8 of 16 had a visual acuity of 20/100 or better and 6 had a visual acuity of 20/30 or better; 3 patients had slight improvement. Visual fields remained stable in 4 patients and improved in the 3 patients who also had slightly better visual acuity. In another study by Egan and Lessell,[26] 54% of 16 patients with ONSMs maintained visual acuity of 20/30 or better during a mean follow-up of 10 years. In a study by Saeed et al.,[27] 35% of patients with ONSMs maintained visual acuity of 20/50 or better during a mean follow-up period of 5.2 years. Because of the benign course of ONSMs, radiation therapy is not necessary in all patients with ONSM and is reserved for those patients whose visual function declines under observation.

In patients with worsening visual acuity, visual field defects, or intracranial extension documented on MRI of the brain, radiotherapy is the treatment of choice to preserve vision and prevent further growth of the tumor. Optic nerve sheath biopsy is rarely required because the diagnosis of ONSM can usually be made by typical radiographic features, but it may be done for atypical presentations of ONSM before radiotherapy is started. Stereotactic and three-dimensional conformal fractionated radiotherapy can deliver radiation more precisely with less risk of complications. It is recommended that 28 daily fractions of 1.8 Gy to 2 Gy per fraction up to a total of 50.4 Gy to 56 Gy is administered over 5 to 6 weeks. Several studies have shown that visual acuity may improve in 36% to 58% of patients, and visual function can remain stable in 42% to 50%.[28–30]

The risk of complications is determined by the delivery method and use of fractions greater than 1.9 Gy. In a retrospective series of 15 patients with primary ONSM,[29] transient problems included local erythema that occurred in 5 patients and local alopecia in 11 patients. Late complications at mean follow-up of 37 months included functional hyperpolactinemia in 1 patient and partial hypophyseal insufficiency in another patient. In another retrospective study by Narayan et al.,[30] mild corneal inflammation was found early in 1 patient, and most other patients had transient alopecia. At a mean of 51 months of follow up, 1 patient had dry eye syndrome, 2 patients had iritis, and 1 patient had grade 2 radiation retinopathy that did not affect vision. Visually significant radiation retinopathy has been reported in a patient who received 48 Gy to 54 Gy to the optic nerve head and 27 Gy to 48 Gy to the posterior retina. Visual acuity progressively worsened from 20/15 at 22 months posttreatment to 20/300 at 4 years posttreatment.[31] Furthermore, radiation optic neuropathy has been seen in patients receiving single doses between 8 and 12 Gy or total doses of more than 50 Gy.[32,33] Therefore, stereotactic and three-dimensional, conformal, low-dose, fractionated radiotherapy for ONSMs appears to improve visual outcome.

Surgery often leads to a poor visual outcome and is reserved for specific circumstances. If significant intracranial extension of the tumor occurs, then surgery is the treatment of choice to prevent involvement of the other eye. If the affected eye is proptotic and blind, then surgery is recommended for cosmetic improvement. To decrease the risk of intracranial extensions or contralateral extension, resection of the tumor and the optic nerve with no salvageable vision

would be reasonable. A variety of surgical procedures, including en bloc excision of tumor with optic nerve, total excision of tumor, tumor debulking, and optic nerve sheath decompression have been described in case series reports. These procedures invariably lead to visual loss if disruption of the pial vasculature that supplies the intraorbital optic nerve is involved. Other surgical complications include bleeding, risk of infection, risks associated with anesthesia, ophthalmoplegia, and ptosis. In a retrospective study of 47 patients by Saeed et al.,[27] en bloc excision of tumor resulted in no detectable recurrence, in contrast to tumor debulking, which was associated with later recurrence. Poor visual outcomes were observed after optic nerve sheath decompression, probably because the pial vasculature was disrupted. In another study in 15 eyes of 11 patients with tumors confined to the optic canal,[34] however, decompression of the canal via craniotomy and without tumor resection led to long-term stable or improved vision.

In contrast to ONSMs that arise secondarily as a result of direct spread from the planum sphenoidale or tuberculum sellae into the optic canal, some meningiomas may rarely arise from extradural ectopic nests of meningeal tissue. In contrast to ONSMs, these tumors separate from the optic nerve dura and can be completely resected without damage to the optic nerve. Visual prognosis in such cases is relatively good.[6,7]

Hydroxyurea has been a chemotherapy option for patients with unresectable recurrent intracranial meningiomas.[35] It has recently been used as an alternative primary treatment for ONSM, as reported in one patient. In the study by Paus et al.,[36] hydroxyurea was administered to a 46-year-old patient with primary ONSM compressing the optic nerve to cause visual acuity of 20/400. After 20 mg/kg/day oral hydroxyurea for 10 months, his visual acuity improved to 20/25. No detectable change in the size of his tumor was seen on MRI. His vision remained stable 18 months thereafter. The side effects of oral hydroxyurea include myelosuppression, gastrointestinal symptoms, blackening of nails, skin rash, and hair loss. In patients who have progressive disease despite radiation therapy, hydroxyurea may be another treatment option. Although meningioma tumor cells have been found to have estrogen and progesterone receptors, hormonal therapy has not been successful. Chemotherapy with progesterone-receptor antagonists, such as RU-486, caused 10% tumor shrinkage in 5 of 14 patients with unresectable meningiomas; visual fields improved in only 1 patient during follow-up of 3 to 31 months. Three patients experienced progression of their tumors.[37]

In children, ONSMs may be more aggressive and require more frequent follow-up and neuroimaging. In a study of 88 patients with ONSMs,[27] 2 of 6 children had NF 2, 2 of 6 had café-au-lait spots, and 3 of 6 developed intracranial extension of the tumor.

A suspected diagnosis of ONSM requires further investigation for NF-2. If NF-2 is associated with ONSM, orbital surgery is recommended when tumor progression is seen on MRI or when the affected eye develops proptosis or pain. If the ONSM presents as an isolated finding in the orbit associated with good vision, then observation for any visual or radiographic progression is recommended. Excision of the optic nerve and even the optic chiasm is preferred if intracranial involvement is documented. Postoperative visual function in these cases is usually poor. As no prior experience has been published for radiation therapy in childhood ONSM, it is not advocated in the pediatric population. Therefore, observation and surgery, when necessary, are the main management strategies for childhood ONSMs.[38]

Compression of the Optic Nerve from Orbital Lesions

Grave's Ophthalmopathy and Optic Nerve Compression

Epidemiology

In a study of 120 patients (103 females) more than 15 years of age, the male incidence of thyroid ophthalmopathy was 3 in 100,000 and

the female incidence was 16 in 100,000. Grave's ophthalmopathy usually presents bimodally at 20 years and 60 years of age.[39] Grave's disease and thyroid opthalmopathy are associated with HLA-DR, B8, and DW haplotypes. A familial tendency also occurs in about 30% of patients, as shown in twin studies.[40] The strongest risk factor for the development of thyroid ophthalmopathy is hyperthyroidism. Smoking has been shown to be a risk factor for the development and progression of this disorder. Thyroid ophthalmopathy is also more severe in women and with advancing age, especially in men.[41]

Symptoms and Signs

Grave's ophthalmopathy is an immune-mediated inflammatory disorder of the orbit associated with diplopia, ophthalmoparesis, and infiltration of extraocular muscles. The compressive optic neuropathy occurs in less than 5% of patients with thyroid disease.[42] In patients with advanced thyroid ophthalmopathy who undergo orbital decompression, optic neuropathy occurs in up to 50% of patients.[43] The likelihood of developing a compressive optic neuropathy from Grave's ophthalmopathy is most significantly correlated with the presence of extraocular motility deficits and periorbital edema at the orbital apex.[43] Unilateral congestive manifestations, such as proptosis, periorbital edema, conjunctival chemosis, and motility limitation, often precede the bilateral, symmetric, gradual visual loss. Most patients have a subtle and insidious onset of visual loss.[44] Some patients may experience more acute visual loss. Other signs of compressive optic neuropathy include afferent pupillary defect and color deficits. The most common visual field defects are central scotomas, arcuate or altitudinal defects, paracentral scotomas, and generalized constriction.[45] In a study of 36 eyes in patients with dysthyroid optic neuropathy,[44] 33% of patients had mild to marked optic disc edema with visual acuities of 20/60 or worse. Fifty percent of patients had normal optic discs and about 17% had pale discs. Horizontal or vertical folds or striae can occasionally be seen at the posterior pole adjacent to the optic disc.[46–48] Less commonly, optic disc edema with peripapillary hemorrhages may be present in patients who experience more acute visual loss.

Thyroid ophthalmopathy is a distinct autoimmune disorder from Grave's hyperthyroidism. The severity of the ophthalmopathy does not correlate with the thyroid function or levels of thyroid-stimulating antibodies.[49,50] Most patients develop eye symptoms within 18 months of onset of hyperthyroidism, but the ophthalmopathy can precede or follow thyroid dysfunction at any time. Thirty-five percent of patients develop thyroid ophthalmopathy more than 6 months after being diagnosed with hyperthyroidism, whereas only 7% develop thyroid ophthalmopathy more than 6 months before having hyperthyroidism. It is estimated that about 40% of all patients with hyperthyroidism will develop thyroid ophthalmopathy at some time.[51,52] Furthermore, the treatment for Grave's hyperthyroidism does not seem to significantly affect the onset or course of Grave's ophthalmopathy.[53]

Diagnostic Testing

Orbital CT scan usually reveals enlargement of the nontendinous portion of the extraocular muscles and can exclude tumors or other orbital pathology as a cause of exophthalmos. In addition to extraocular muscle enlargement and sparing of the tendons, orbital CT scans can demonstrate propotosis, lacrimal gland enlargement, and eyelid soft tissue edema. Low-density areas in the eye muscles could represent glycoaminoglycan deposition or fatty infiltration in more chronic cases.[54] MRI of the orbits with short tau inversion recovery (STIR) and gadolinium sequences may also demonstrate greater detail of the enlarged muscles in the apex of the orbit to mimic an orbital apex tumor, especially on axial sections. STIR sequences can detect high water content in tissues representing inflammation or active disease. The signal intensity of enlarged muscles is low on T_1-weighted imaging and appear isointense to fat on T_2-weighted imaging. The surrounding enlarged muscles can be seen apposing the optic nerve

in the orbital apex in patients with optic neuropathy.[42,43]

Pathology

In early thyroid ophthalmopathy, the nontendinous portion of the extraocular muscles have interstitial edema and an inflammatory infiltrate, consisting of B cells more than T cells.[55] These inflammatory stimuli cause endomysial fibroblasts to produce mucopolysaccharide, such as hyaluronic acid.[56] The muscle fibers themselves later become edematous and inflamed. In later stages of severe thyroid ophthalmopathy, the fatty infiltrated and fibrosed muscle causes a restrictive myopathy. The inflammation and increase in orbital fat contribute to a mechanical compression of the optic nerve.[57] The optic nerve is not stretched, because the degree of exophthalmos is not correlated with the severity of optic neuropathy.[42] Histopathological specimens of compressed optic nerves show a decrease in neurofilaments in the axons[56] that is consistent with a compressive optic neuropathy. CT studies have shown that increased extraocular muscle volume is associated with optic neuropathy,[43,50] and improvement of the optic neuropathy appears to correlate with a decrease in extraocular muscle enlargement at the apex of the muscle cone.[42]

Management

Visual loss from compressive optic neuropathy is an emergent ocular complication of thyroid eye disease. Corticosteroids are considered the treatment of first choice. In a randomized study of 15 patients with active Grave's ophthalmopathy,[58] 82% of patients who underwent surgery did not respond because of persistent visual loss and chemosis; these patients then required further immunosuppressive therapy. Only 45% of the patients who underwent intravenous methylprednisolone pulses for 2 weeks followed by oral prednisone for 4 months did not improve in visual acuity and needed decompressive surgery. When patients failed their initial therapy and were switched to the other treatment arm, visual acuity usually improved. In a prospective, single-blinded, randomized study of 82 patients with Grave's ophthalmopathy,[59] 87.8% of patients who underwent orbital radiotherapy and IV corticosteroids compared to 63.4% of patients who had orbital radiotherapy and oral corticosteroids experienced decreased proptosis. Although diplopia improved in both groups, there was no statistically significant difference between the two groups. Compressive optic neuropathy improved in 11 of 14 patients who received IV corticosteroids and in only 3 of 9 treated with oral corticosteroids. The rate of side effects with IV corticosteroids was lower than that with oral corticosteroids.[59,60]

If vision improves with corticosteroids, radiation therapy may be considered as a steroid-sparing modality. A total dose of 2000 cGy is administered in 10 fractions over 2 weeks. Improvement in periorbital edema, extraocular motility, and optic neuropathy may be seen from weeks to months after the radiation treatment. Radiation therapy does not affect proptosis and does not prevent progression of the disease.[53] It has been shown that the combination of orbital radiotherapy and high-dose systemic corticosteroids provides a more favorable response in severe Grave's ophthalmopathy than orbital radiotherapy alone.[59]

If methylprednisolone pulse therapy or radiation therapy fails, then posterior orbital decompression surgery should be considered. Studies have shown that surgery involving at least two walls, the orbital floor and medial wall, or in more severe cases, three walls, the orbital floor, medial wall, and lateral wall, is effective in improving vision.[61] In a study of 48 eyes that had transantral orbital decompression after failing corticosteroids, 77% had improved visual acuity, 17% were stable, and 6% worsened.[62] The most common complication is diplopia.[63,64] In a study of 17 patients with Grave's ophthalmopathy who were not responsive to medical treatment,[65] endonasal endoscopic orbital decompression improved visual acuity, decreased proptosis, and intraocular pressure. Postoperative diplopia was managed by eye muscle surgery or by application of prisms. In another study by Shepard et al.,[66] endoscopic

medial decompression with a lateral decompression with preservation of the medial orbital strut between the ethmoid cavity and the orbital floor could minimize the risk of diplopia.

Idiopathic Orbital Inflammatory Pseudotumor

Epidemiology

Idiopathic orbital inflammatory pseudotumor may also cause compression of the proximal optic nerve and secondary optic disc edema. It is a nongranulomatous process limited to the orbit with no identifiable cause. Its incidence is approximately 9% of all orbital mass lesions. There is no sexual predilection, but it often occurs between 40 to 60 years of age.[67]

Symptoms and Signs

Acute, recurrent, or chronic orbital pain, conjunctival redness, diplopia, and decreased vision are the most common symptoms. In contrast to thyroid ophthalmopathy, pain in idiopathic orbital pseudotumor is often unilateral and is more acute and worsens with eye movements. Patients usually present with signs of unilateral proptosis, ptosis, ocular motility deficits in the field of the inflamed muscle, and good vision. If the inflammation worsens, then a compressive optic neuropathy may develop and manifest as decreased visual acuity, visual field defects, afferent pupillary defect, color deficits, and optic disc edema.[67] In contrast, eyelid retraction and restrictive eye movements with impaired vision are more often seen in thyroid ophthalmopathy.[52]

Diagnostic Testing

To screen for inflammatory/autoimmune systemic disorders that may cause orbital inflammatory pseudotumor, serum syphilis serology, antinuclear antibody (ANA), angiotensin-converting enzyme (ACE), antineutrophilic cytoplasmic antibody (ANCA) levels, and a chest X-ray should be performed. Orbital CT scan commonly reveals a thickened posterior sclera, uvea, and lacrimal gland.[67] The extraocular muscles and tendons are also enlarged. Perioptic infiltration leads to optic nerve sheath enlargement. Inflammatory infiltrates also extend into the orbital fat. Because orbital inflammatory pseudotumor may involve single or multiple muscles and may be well circumscribed, it can mimic an orbital tumor.[68] On MRI, orbital inflammatory pseudotumor is often isointense to muscle on T_1-weighted images and isointense to orbital fat on T_2-weighted images.[69] If the orbital inflammation occurs in a patient who has a history of malignancy or if it is recurrent or atypical in appearance, then a biopsy should be considered for definitive diagnosis. Otherwise, the diagnosis of idiopathic orbital inflammatory pseudotumor is one of exclusion.[68]

Histopathology

The inflammation is often localized to the ocular muscles, lacrimal glands, and orbital vessels. Idiopathic orbital inflammatory pseudotumor can be quite variable in presentation, either with numerous types of cells or with predominantly collagen and a few cells. The major hallmark features include the following: (1) cellular polymorphism, consisting of lymphocytes, plasma cells, histiocytes, and eosinophils; (2) lymphoid follicles with germinal centers; (3) absence of atypia; and (4) ancillary evidence of inflammation, such as plasmacytoid cells and capillary proliferation with swollen, enlarged endothelial cells.[67]

Management

Prednisone 80 mg to 100 mg daily is the initial treatment of choice. If vision does not respond or if the inflammatory pseudotumor recurs during taper, low-dose radiation may then be administered.[67] In contrast to thyroid ophthalmopathy, which may respond to steroids slowly, idiopathic orbital pseudotumor responds immediately and resolves completely. In patients who are refractory to corticosteroids and who do not have other identifiable disorder, cyclophosphamide or cyclosporine may be used as adjunc-

tive therapy. Orbital radiation therapy may also be considered as an alternative treatment.

Sellar and Suprasellar Compressive Lesions on Optic Nerve and Chiasm

See Table 4.1.

Pituitary Adenoma

Epidemiology

Of all the masses that present within the pituitary sella, pituitary adenomas are the most common type of tumors, which may account for 10% to 20% of all intracranial tumors.[70] There is no sexual predilection, but they are most common in adults during 30 to 40 years of age. These tumors are not hereditary, for their association is with multiple endocrine adenomatosis, an autosomal dominant disorder.

Symptoms and Signs

Bilateral visual field defects, especially bitemporal ones, are the hallmark of a chiasmal lesion, such as a pituitary adenoma. The pituitary adenoma can compress the distal optic nerve on one side near its junction with the optic chiasm and also compress the inferior nasal fibers from the contralateral eye before continuing posteriorly into the chiasm. This type of structural compression produces an anterior chiasmal syndrome or distal optic nerve syndrome. Damage to the distal optic nerve causes an ipsilateral decrease in visual acuity with a color defect, relative afferent papillary defect, and possible temporal field loss. Eventually the optic disc becomes pale. Damage to the contralateral inferior nasal fibers causes a superior temporal field defect without evidence of an optic neuropathy. Rarely does a pituitary adenoma compress a postfixed chiasm to cause monocular visual loss. The decreased central visual acuity is often associated with central or arcuate scotomas.[71,72]

Neuroimaging

MRI of the brain allows visualization of tumors up to less than 1.0 cm in diameter. Pituitary adenomas can invade the dura or bone and may infiltrate surrounding structures. Locally invasive pituitary adenomas are often histologically benign. Macroadenomas, defined as greater than 1.0 cm in diameter, are usually the type

Table 4.1. The age range, causes, and relative frequency of sellar and suprasellar compressive lesions

Age group	More common	Less common
Pediatric to young adult	• Chiasmal-hypothalamic glioma • Craniopharyngioma	• Arachnoid cyst • Arteriovenous malformation • Choristoma • Dermoid cyst • Empty sella syndrome • Ganglioglioma • Germ cell tumors • Pituitary adenoma • Rathke's cyst
Middle-aged to older adult	• Aneurysm (internal carotid) • Craniopharyngioma • Meningioma • Pituitary adenoma • Pituitary apoplexy	• Malignant optic glioma • Metastases to chiasm, sella, or suprasellar region • Spheno-ethmoidal mucocele
At any age range		• Histiocytosis • Lymphocytic hypophysitis • Meningitis-bacterial, tuberculous • Sarcoidosis

Source: Adapted from Richardson.[70]

that grow large enough to affect the visual pathways. These benign tumors may extend superiorly to contact and/or compress the optic chiasm. Compression of the chiasm inferiorly results in bilateral superior temporal quadrantanopsia. As the tumor enlarges, the field defect progresses to a complete bitemporal hemianopsia. If the optic chiasm is prefixed, pituitary tumors compress the optic tract and posterior chiasm. If the optic chiasm is postfixed, pituitary tumors affect the optic nerve and anterior chiasm.[73,74]

In a study of 27 patients with pituitary macroadenomas,[75] 9 patients demonstrated unilateral optic nerve hyperintensity lesions on T_2-weighted MRI, whereas 5 patients revealed bilateral signal intensity abnormality of the optic nerve at the site of compression and in the ventral aspect of the tumor. Abnormal hyperintensity of the optic nerves ventral to the pituitary macroadenoma was associated with the degree of visual acuity impairment. Recovery of visual acuity was also correlated to disease duration. MRI of the optic nerves may play a role in monitoring and managing visual outcome.

Pathology

Pituitary adenomas can be either secretory or nonsecretory. Null cell adenomas or nonsecreting adenomas are more common and demonstrate no clinical or immunohistochemical evidence of hormone secretion. Secretory adenomas are less common and produce one or more anterior pituitary hormones, including prolactin, as the most common, growth hormone, ACTH, follicle-stimulating hormone, or luteinizing hormone. Pituitary carcinomas are exceedingly rare and usually require distant metastases to establish this diagnosis.[70]

On histology, pituitary adenomas appear as a sheet of follicular, trabecular, or cystic components with foci of hemorrhage or necrosis, but no mitoses. The tumor has a pseudocapsule that facilitates surgical separation from the adjacent normal gland.[70]

Management

The most commonly used medical therapy is oral dopamine (D_2) receptor agonists, such as bromocriptine, cabergoline, and quinagolide, in managing prolactinomas. These medications limit prolactin secretion and reduce prolactinoma size. Reduction of tumor size and improvement of visual fields may occur within hours of starting treatment, but poor response to this treatment requires surgical resection. In macroprolactinomas that are greater than 10 mm in diameter, bromocriptine has been reported to maintain remission for 5 years in 5% to 15% of patients. Cabergoline and quinagolide are newer drugs with fewer side effects than bromocriptine, which can cause nausea and orthostatic hypotension. In microprolactinomas that are less than 10 mm in diameter, the use of D_2 agonists has been controversial because their natural history is still incompletely defined.[70]

If the tumor is not a prolactinoma, then surgery would be the initial treatment of choice for pituitary adenomas. According to a study on 53 patients who underwent transphenoidal surgery, visual field defects improved in 89% of the patients and visual acuity improved in 82%.[75] In a retrospective analysis of 35 patients by Randeva et al.,[76] transphenoidal surgery for pituitary apoplexy resulted in significantly greater improvement in visual acuity and fields when it was performed within 8 days compared to surgery after this time period. In a report of 15 patients by McFadzean et al.,[77] high-dose steroids along with radiotherapy followed by surgical resection resulted in postoperative visual acuity improvement in 10 of 15 patients; only 2 were unchanged.

Radiotherapy is an alternative when surgery is not an appropriate initial step. Postoperative radiation is used for certain tumor histologies for which remission and recurrence rates after operative resection can be reduced with combined therapy. Although postoperative radiation is still used to treat residual tumor after resection of pituitary adenoma, it is no longer routinely given to patients after resection of nonsecretory adenomas or to those in whom endocrine measures are normal. The improved resolution on MRI and newer endocrine measures allows a more expectant management approach in which radiation is reserved for patients with evidence of tumor

growth or endocrine evidence of recurrent hypersecretion.[70]

Pituitary Apoplexy

Epidemiology

The incidence of pituitary apoplexy ranges from 5% to 16.6% in patients with a preexisting pituitary adenoma. It affects males to females in a ratio of about 1 to 9.[78]

Symptoms and Signs

Pituitary apoplexy, infarction, and hemorrhage of the pituitary gland is a neuro-ophthalmic emergency. Pituitary apoplexy is characterized by sudden onset of severe headaches with vomiting, other signs of meningeal irritation, and followed by visual loss. In studies by Muller-Jensen and Ludecke[78] and Ahmed et al.,[79] a decrease in visual acuity and central scotoma, affecting one eye more than the other, was commonly seen. The classical bitemporal field defect was absent in 50% of those with perimetry. Compressive ischemic damage from the preexisting tumor can occur in the intracranial portions of the optic nerves, the optic chiasm, and the optic tracts.[73] Third nerve palsies as part of an external ophthalmoplegia occur in more than 50% of patients as a consequence of compressive ischemia from tumor or hemorrhage in the cavernous sinus, subarachnoid space, or brainstem.[80]

Pathogenesis

The high metabolic demand of the normal pituitary gland, along with the tenuous blood supply through a portal (double-capillary) vascular system, predisposes the gland to infarction in situations where blood supply is compromised. Pituitary apoplexy may occur in the setting of pituitary tumor growth, leading to high metabolic demand and increased pressure within the sella, causing a critical reduction in blood flow. Apoplexy may also occur in pregnant women at the time of delivery (Sheehan's syndrome). The physiological hypertrophy of the gland associated with pregnancy produces predisposing conditions analogous to those seen with pituitary tumors. At delivery, transient hypotension may precipitate the crisis, resulting in infarction. With a normal gland and no erosion in the sella, the neuro-ophthalmic manifestations, other than a headache, may be subtle or absent, and Sheehan's syndrome may be unrecognized until hypopituitarism becomes evident after delivery with failure of lactation or postpartum amenorrhea.[70]

Neuroimaging

MRI is more sensitive than CT in detecting pituitary apoplexy. MRI reveals a macroadenoma with heterogeneous signals representing hemorrhage whereas routine CT shows an unenhancing, hyperdense sellar mass. Lumbar puncture should also be performed to rule out subarachnoid hemorrhage. If cerebrospinal fluid (CSF) red blood cells are present, a cerebral angiogram should be done to screen for a ruptured aneurysm in the sellar region if the CT and MRI results are inconclusive.

Treatment

Because most patients have hypopituitarism, high-dose corticosteroids should be administered. The patient needs to be stabilized with appropriate hormonal replacement therapy by an endocrinologist and then needs to be evaluated for transphenoidal tumor resection.[77] Although some patients spontaneously improve, those who undergo surgery within 1 week usually experience improvement in their visual acuity, visual fields, and ocular motility problems.

Suprasellar Meningioma

Epidemiology

Suprasellar meningiomas represent 3% to 10% of all meningiomas.[81] Women are more commonly affected than men, and most patients are between 30 and 60 years of age.[81]

Symptoms and Signs

Most patients present with suprasellar meningiomas present with painless, asymmetric

progressive loss of visual acuity.[81] These tumors tend to cause asymmetric compression of the optic nerves.[82] Some patients may present with unilateral visual symptoms representing an optic neuropathy but actually also have a milder contralateral optic neuropathy with only signs of slightly decreased visual acuity, decreased color vision, and visual field defects.[83]

Visual field defects may include arcuate defects, altitudinal defects, central scotomas, and peripheral constriction.[84] Less often seen is the distal optic nerve syndrome in which the patient has unilateral visual loss and a junctional scotoma, a superior temporal field defect in the contralateral, asymptomatic eye.[82] In patients with postfixed optic chiasms, suprasellar meningiomas may grow between the optic nerves to compress them against the internal carotid arteries.[85] Compression of the temporal fibers of the intracranial areas of both optic nerves results in binasal visual field defects. If the optic chiasm is compressed, asymmetric bitemporal visual field defects usually occur. When suprasellar meningiomas extend posteriorly or when the optic chiasm is prefixed, damage to the optic tract results in a homonymous hemianopia. A pure optic tract syndrome is very rare, and the optic tract lesion is often associated with an additional optic neuropathy. Optic disc swelling, as part of a Foster–Kennedy syndrome or a cavernous sinus syndrome, is seen more commonly in suprasellar meningiomas that arise from the anterior clinoid process.[82]

On funduscopic examination, optic atrophy is often seen. Sometimes optic nerves may appear normal. Based on the study of 18 patients by Chicani and Miller,[84] 17% of patients had normal optic discs, 39% had bilateral optic disc pallor, and 44% had one normal disc and one pale disc. If suprasellar meningiomas become large to produce increased intracranial pressure, then papilledema may develop with unilateral or bilateral sixth nerve palsies.

Neuroimaging

The MRI features of a suprasellar meningioma include the suprasellar epicenter, tapered dural base, and bright enhancement with gadolinium that differentiates it from a pituitary adenoma. Magnetic resonance angiography (MRA) or cerebral angiography often reveals a tumor blush that is characteristic of a meningioma, but this may also occur in pituitary adenomas.[86]

Pathology

Suprasellar meningiomas often arise from arachnoid granulations overlying the dura of the tuberculum sellae and continue to compress and displace, rather than invade adjacent brain. Some can also arise from the diaphragma sellae.[87,88] Meningiomas from the tuberculum sellae and diaphragma sellae are located in the retrochiasmatic region and can grow to compress the visual pathways.[88] Meningiomas are commonly a combination of the transitional form, composed of whorls and psammoma bodies, and the syncytial type, composed of sheets of polygonal cells. The fibroblastic type of meningioma consists of spindle cells with collagen. The more aggressive variants include the papillary, angioblastic, and anaplastic types.[89]

Course and Visual Prognosis

The visual prognosis in patients with suprasellar meningiomas is influenced by the duration of visual symptoms before tumor resection, tumor size, and preoperative visual function. In a recent study of 18 patients with suprasellar meningiomas, Chicani and Miller[84] showed that about 80% of eyes in patients treated within 1 year of onset of symptoms improved or remained stable after surgery, whereas 70% of eyes in patients treated more than 1 year after symptom onset either worsened or remained stable. After 10 years or more of postoperative follow-up, 72% of patients had visual acuity of 20/40 or better in at least one eye. Previous studies, such as those of Gregorius et al.[90] and Rosenberg and Miller,[83] have shown that a shorter duration of visual symptoms is associated with better preoperative visual function and smaller tumor size. Tumors restricted to the tuberculum sellae had a better outcome than those that extended to other areas. The average postoperative mortality in most reported series of suprasellar meningiomas was 10%.[83]

Management

The treatment of choice for suprasellar meningiomas, regardless of size, is surgical resection, but recurrence is common even after total tumor removal and after 10 years or more. The recurrence rates for suprasellar meningiomas range from 5% to greater than 30%.[91–95] Radiation therapy, such as three-dimensional conformal fractionated radiation therapy and stereotactic radiosurgery, should be started shortly after surgery to attain the best visual outcome.[96–100] It has been recommended that postoperative patients with complete resection still be monitored on a long-term basis with serial eye examinations and neuroimaging for any recurrences to allow the opportunity for early and aggressive treatment. Patients with incomplete resection of their suprasellar meningiomas should undergo postoperative radiation therapy.[84]

In older patients with minimal visual loss over a long period of time, observation may be appropriate because meningiomas are benign and slow growing. Chemotherapy with progesterone-receptor antagonists, such as RU-486, and interferon-alpha have been unsuccessful in the past. For malignant meningiomas, novel angiogenesis inhibitors are being studied.[101]

Sphenoid Wing Meningioma

Epidemiology

Meningiomas en plaque of the sphenoid wing constitute about 4% of all meningiomas.[102] They affect women three to six times more often than men during the ages of 40 to 50 years.

Symptoms and Signs

Slow tumor infiltration of the orbit causes a slowly progressive unilateral proptosis as the most common initial symptom, but optic neuropathy is the most common cranial nerve palsy.[103]

Vision is correlated with the location of the tumor in which intraconal or extraconal involvement is associated with worse visual acuity. Optic nerve compression usually occurs late and is related to compression of the orbital portion of the optic nerve. In a retrospective study of 67 patients with meningiomas en plaque originating from the sphenoid wing,[104] 28 presented with decreased visual acuity, 7 with blindness, and 24 with visual field defects. Temporal hemianopias, superior temporal defects, and inferior temporal defects were most common. Other less common defects included central scotomas, peripheral constriction, and superior nasal defects. Optic disc pallor was seen in 10 patients, and disc edema was observed in 3 patients.

Neuroimaging

This slow-growing tumor infiltrates the sphenoid bone and the dura. The hyperostosis of the sphenoid wing and optic canal is best seen on high-resolution CT scan. MRI scan demonstrates the extent of infiltration of the dura mater and intracranial extension.[101]

Pathology

Please see section on suprasellar meningioma pathology.

Management

The treatment for sphenoid wing meningiomas is early surgical resection to prevent recurrence. Aggressive resection of the cavernous sinus and superior orbital fissure infiltrated by tumor is not recommended because of the high risk of morbidity. Radiation therapy is reserved for recurrences or subtotal resections. As recurrence rates range between 4% and 20% in patients with complete excision and up to 50% in those with subtotal resection, long-term monitoring of this tumor is needed over a 10- to 20-year period.[104]

Craniopharyngioma

Epidemiology

Craniopharyngiomas are suprasellar tumors that commonly manifest in childhood. Craniopharyngiomas are the most common brain tumors of nonglial origin in children, representing about 3% to 6% of all childhood tumors.

The age of incidence is bimodal, occurring more commonly in patients less than 18 years of age and less often between 50 and 70 years.[105]

Symptoms and Signs

Children and adolescents often develop symptoms and signs of increased intracranial pressure and hypothalamic-pituitary defects, such as growth failure, obesity, diabetes insipidus, slow sexual development, heat dysregulation, spontaneous pain, and vasomotor disturbances related to thalamic dysfunction.[106] Most develop visual loss and may not be detected until they have secondary strabismus or other symptoms.[107]

Adults with craniopharyngiomas develop gradual progressive visual loss and mental status changes.[108] In a retrospective study of 74 patients by Baskin and Wilson,[108] 88% of men over 18 years of age presented with impotence and 82% of women over 18 years of age presented with either primary or secondary amenorrhea, often with galactorrhea. Compression of the tumor onto the hypothalamus or pituitary stalk most commonly leads to deficiencies in growth hormone, gonadotropin, cortisol, and thyroid-stimulating hormone and in elevated serum prolactin levels.[109,110]

Most patients with craniopharyngiomas develop visual field defects. In the series by Baskin and Wilson, 72% had field defects, including bitemporal hemianopia, homonymous hemianopia, and bilateral optic nerve defects.[108] Similar to other suprasellar tumors, craniopharyngiomas cause progressive unilateral or bilateral decrease in visual acuity associated with other evidence of optic neuropathy. The visual field defects are variable and may include central scotomas, cecocentral scotomas, paracentral scotomas, arcuate scotomas, and nasal or binasal defects.[111] If the tumor is compressing the optic nerves from below or from either side in a patient with a postfixed chiasm, then a unilateral or bilateral optic neuropathy develops. A "junctional or anterior chiasmal syndrome" is occasionally formed by a unilateral distal optic neuropathy associated with a superior temporal field defect in the asymptomatic contralateral eye. Bitemporal field defects occur in 25% to 50% of patients with craniopharyngiomas from compression of the optic chiasm.[108] These field defects may occur with normal visual function or decreased visual acuity and color vision. If the tumor compresses the optic tract, an incomplete and incongruous homonymous hemianopia may be seen.[108]

At the time of diagnosis, the fundus may be normal. As the tumor directly compresses the anterior visual system or displaces the nerves against the internal carotid or anterior cerebral arteries, optic atrophy gradually develops. Papilledema is most often seen in children and adolescents when the tumor has extended into the third ventricle.[112]

Ocular motility deficits may appear when craniopharyngiomas cause increased intracranial pressure and compress the subarachnoid portions of the nerves or the brainstem.[113] Seesaw nystagmus is probably a result of compression of the mesencephalon, especially the nucleus of Cajal or its connections.[114]

Neuroimaging

CT scans typically show a cystic-appearing lobulated suprasellar mass with a solid mural nodule. Nodular or rim calcification is seen in almost all children with craniopharyngiomas and in about half of all adults. Cyst contents are usually higher in attenuation than the CSF. With contrast administration, nodular or rim enhancement is usually present. The MRI signal characteristics of craniopharyngiomas vary depending on the tumor composition of cystic and solid components. MRI of the brain usually reveals a cyst that is hypointense on T_1- and hyperintense on T_2-weighted sequences. The increased signal intensity on T_1-weighted images represents high protein concentration and/or degraded blood products. With contrast administration, craniopharyngiomas enhance heterogeneously.[115] An MRI with sagittal views and a CT with coronal views should be done for optimal imaging before surgery.

Pathology

Craniopharyngiomas are cystic, calcified benign tumors and are thought to arise from the vesti-

gial nests of squamous cells that are often found at the junction of the lower infundibular stem and the pars distalis of the adenohypophysis. The failure of complete involution of the hypophyseal pharyngeal duct tract leads to the development of the craniopharyngioma.[116] The tumors vary from small, solid, well-circumscribed nodules to large multinodular cysts that invade the sella turcica and displace adjacent brain structures. The cysts are filled with a turbid fluid containing cholesterin crystals. The three histological types of craniopharyngioma are (1) mucoid epithelial cysts lined with ciliated columnar and mucus-secreting cells; (2) squamous epitheliomas consisting of islands of squamous epithelium with cystic degeneration; and (3) adamentinomas consisting of epithelial masses forming a reticulum of teeth-like structures.[117]

Management

Patients usually undergo primary total resection or limited surgery of the tumor followed by radiation therapy. Postoperative damage to the optic chiasm, vasculature, and hypothalamus appears to be higher in patients undergoing total resection. Patients undergoing incomplete resection of the tumor followed by radiation therapy often have better survival rates and lower rates of endocrine deficits and neovascular and hypothalamic injury.[118] Tumor recurrence is usually treated with radiation therapy because further surgery is associated with tumor spread and recurrence and increased morbidity and mortality. Radiation optic neuropathy and cerebral radionecrosis and other complications are becoming more rare because of three-dimensional conformal radiation therapy, stereotactic radiosurgery, stereotactic radiotherapy, and intensity modulated radiation therapy.[118]

Postoperative visual prognosis for patients with craniopharyngioma depends mostly on the severity of visual damage that has occurred before treatment and the extent of manipulation of the optic nerves and chiasm at the time of surgery. In the study of 22 patients with resected craniopharyngiomas,[119] children (50%) more often presented with optic atrophy than adults (30%). Visual loss may be difficult to detect in children until severe stages. Postoperative visual acuity was 20/40 or better in 67% and worse than 20/40 in 33%.

Internal Carotid or Anterior Communicating Artery Aneurysm

Internal carotid aneurysms can compress the intracranial portion of the optic nerve to cause a gradually progressive unilateral or bilateral optic neuropathy. It may present as an "unexplained" optic neuropathy in some cases. Visual acuity decreases very slowly. Visual field defects reflecting nerve fiber bundle defects are most common. In 25% of patients, a central scotoma or absolute central visual field is seen. Affected optic discs are excavated, mimicking glaucomatous change. A coronal MRI scan can help confirm compression of the affected optic nerve.[120]

Almost one-third of all intracranial aneurysms are located at the anterior communicating artery and present with subarachnoid hemorrhage. Unruptured aneurysms may cause slowly progressive or sudden-onset visual loss associated with headache or ocular pain. The midline location of the anterior communicating artery may cause compression of one or both optic nerves, in addition to the optic chiasm and optic tract.[121–124] Local compression of the optic nerves is uncommon, but 6 of 78 patients with anterior communicating aneurysms had signs of optic neuropathy.[125] In a study by Peiris and Ross Russell,[126] an unruptured anterior communicating artery aneurysm produced a unilateral optic neuropathy in 2 of 5 patients, a bilateral optic neuropathy in the third patient, a unilateral optic neuropathy with a chiasmal syndrome in the fourth patient, and a unilateral optic neuropathy and optic tract syndrome in the last patient. Anterior communicating artery aneurysms can present as a progressive bilateral optic neuropathy or as a sudden unilateral optic neuropathy.[127] Based on pathological studies by Chan et al.,[122] leakage of the anterior communicating artery aneurysm into the optic nerve parenchyma can lead to acute monocular visual loss.

Carotid-Ophthalmic Artery Aneurysm

Most carotid-ophthalmic artery aneurysms arise from the junction of the internal carotid artery and ophthalmic arteries and rarely from the distal portion of the ophthalmic artery itself.[128,129] Aneurysms that are located intracranially, or in the intraorbital area of the vessel, may enlarge the optic canal to cause ipsilateral compressive optic neuropathy.[130] Most patients present with gradual progressive unilateral visual acuity and visual field loss. Aneurysms that arise within the orbit may be asymptomatic[131] or may compress the adjacent optic nerve to cause sudden, fluctuating, or progressive visual loss. Rarely are acute monocular visual loss and proptosis seen from orbital hemorrhage.[132] Direct penetration of the optic nerve by a carotid-ophthalmic artery aneurysm has been documented on MRI.[133] Cerebral angiography revealed the aneurysm to be 12 mm × 7 mm directed superomedially into the optic nerve. Even splitting of the optic nerve has been reported.[133]

Aneurysms of the ophthalmic artery itself are very rare. A ruptured ophthalmic artery aneurysm caused only headache,[135] while an unruptured one completely penetrated the optic chiasm to cause rapid visual loss to count fingers and a nasal hemianopsia in the left eye and an upper temporal quadrant hemianopsia in the right eye. Intraoperative findings revealed complete penetration of the optic chiasm by the fundus of the aneurysm. The patient recovered visual acuity, but visual deficits persisted.[136]

Sphenoid Sinus Mucocele

Patients with sphenoid sinus mucocoeles often present with fronto-orbital pain, visual loss, and cranial nerve palsies involving III or VI.[137–140] Most patients with sphenoid sinus mucoceles develop slowly progressive cranial neuropathies. When the lesion compresses one or both optic nerves, patients may have slowly progressive visual loss.[137,141–143] Occasionally sudden visual acuity and visual field loss can occur mimicking retrobulbar optic neuritis, especially when the patient has associated ocular pain and no evidence of an orbital mass on neuroimaging studies.[142,144–146]

On neuroimaging, the sphenoid sinus mucocele appears as a cystic lesion of high intensity in the sphenoid sinus. Compression of the optic nerve may be seen as a ring of hyperintensity on STIR images demonstrating possible CSF in the dilated perioptic subarachnoid space or compressive edema. This ring of hyperintensity usually disappears after surgical decompression of the mucocele.[146]

Sphenoid sinus mucoceles may expand to displace one or both optic nerves or the optic chiasm, in addition to displacing the cavernous portion of the internal carotid artery, the planum sphenoidal, and pituitary gland; eroding the clivus and spread to the superior orbital fissure and invading the posterior orbit.[147] The mucocele may involve the orbit to cause an acute restrictive ophtahlmoplegia and even proptosis.[148]

Prompt transphenoidal microsurgical decompression of the sphenoid sinus mucocele and antibiotic therapy are necessary to recover good vision.[148] If surgery is delayed more than 7 to 10 days, the visual prognosis becomes poor.[149]

Fibrous Dysplasia

Epidemiology

Fibrous dysplasia is a nonhereditary, nonmalignant skeletal developmental anomaly of the bone-forming mesenchyme that manifests as a defect in osteoblastic differentiation and maturation. The exact incidence of this bone disorder is unknown. It manifests most often between 3 to 15 years of age. Between 10% and 50% of patients have the craniofacial form in which abnormal bone growth in the optic canal can cause a progressive, compressive optic neuropathy.[150–154]

Symptoms and Signs

Most patients with craniofacial fibrous dysplasia involving the sphenoid bone present with a compressive optic neuropathy, manifesting as acute or gradual visual loss associated with an afferent pupillary defect, and a central scotoma or cecocentral scotoma. The optic disc may appear normal.[155–158]

Neuroimaging

Clinical features and neuroimaging can help establish the diagnosis of fibrous dysplasia. CT demonstrates the extent of the disease in the craniofacial region. The expansion of the affected bone and matrix of the lesion with subtle, nondisplaced fractures can be seen. Areas of granulation tissue of the lesion may be seen as decreased density in the sphenoid body or root of the lesser wing on CT scan that can erode into the medial wall of the optic canal.[159] MRI is useful in showing malignant change or extension of the tumor into the optic canal to compress the nerve.[160]

Pathology

Fibrous dysplasia consists of scattered areas of immature woven trabeculae surrounded by a matrix of fibrous tissue. The trabeculae are immature and not lined with osteoblasts. The fibrous stroma is disorganized and replaces the normal marrow. This bone disorder has been attributed to mutations on a G-protein subunit causing abnormal osteoblastic function and, therefore, the formation of abnormal bone matrix.[150]

Management

In cases of acute visual loss, several reports have shown that administration of systemic corticosteroids can help improve vision transiently before the patient undergoes surgery.[155,158] Optic nerve decompression is a controversial treatment modality in traumatic optic neuropathy and in the prophylaxis of compressive optic neuropathy in fibrous dysplasia. It is less controversial for the treatment of optic nerve compression in fibrous dysplasia. Progressive visual loss and sudden visual loss in patients with sphenoidal fibrous dysplasia are considered absolute indications for undergoing optic nerve decompression. This procedure must be done within 1 week from the onset of visual symptoms to reverse visual loss.[161] Optic nerve decompressive surgery should be considered as prophylaxis in the following situations: (1) patients presenting within 2 to 3 weeks of rapid visual loss; (2) children and adolescents with no visual loss but radiographic evidence of optic canal stenosis; or (3) adult patients with no visual loss, radiographic evidence of optic canal stenosis, and evidence of continued active fibrous dysplasia. The recurrence rate after optic nerve decompression for fibrous dysplasia has not been widely reported. Regrowth of the tumor is less likely as more walls of the optic canal are decompressed.[161]

Infiltrative Optic Neuropathies

See Table 4.2.

Primary Tumors Infiltrating the Optic Nerve

Benign Anterior Visual Pathway Gliomas

Incidence

Optic gliomas are relatively uncommon, accounting for less than 5% of all intracranial

TABLE 4.2. Some causes of infiltrative optic neuropathies

Infiltration from primary tumors

- Optic glioma: benign or malignant
- Ganglioglioma

Infiltration from secondary tumors

- Metastatic carcinoma
- Anterior extension of retrobulbar optic nerve tumors: optic nerve sheath meningioma
- Lymphoreticular tumors: lymphoma, leukemia, myeloma, and others
- Tumors of the sensory retina and medullary epithelium: retinoblastoma, medulloepithelioma
- Vascular tumors of the retina: capillary hemangioma, cavernous hemangioma, racemose hemangioma
- Glial tumors of the retina: astrocytic hamartoma
- Melanocytic tumors: melanocytoma, malignant melanoma, combined hamartoma of the retina and retinal pigment epithelium

Infiltration from infections and inflammations

- Sarcoidosis
- Idiopathic perioptic neuritis
- Parasites
- Viruses
- Fungi

Adapted from Miller and Newman.[162]

pediatric tumors and less than 4% of all intrinsic optic nerve tumors that present primarily among children in the first decade of life.[163] Optic nerve gliomas usually occur at 9 years of age, and chiasmal gliomas often occur at 7 years of age.[164] Hypothalamic gliomas, causing a diencephalic syndrome, often present at 1 year of age.[164] Based on data from 1278 cases, approximately 75% of gliomas involve the chiasm, whereas 25% are confined to only the optic nerve.[164]

Optic Gliomas Associated with Neurofibromatosis Type I

The prevalence of NF-I neurofibromatosis type I (Table 4.3) in patients with gliomas of the anterior visual pathway ranges from 10% to 70%.[164] This estimate is influenced by the age of the population investigated because the stigmata of NF-1 becomes more apparent with increasing age.[165] As 36% of optic gliomas related to NF-1 are diagnosed in children over 6 years of age, these children with NF-1 should undergo yearly eye examinations. According to the retrospective study on 54 NF-1 patients by Thiagalingam et al.,[166] yearly eye examinations should be extended in patients with NF-1 up to at least 17 years of age, and those with known chiasmal gliomas should be monitored into adulthood. Another study also reports that late-onset tumors can develop as late as the third decade of life and are more likely to progress after diagnosis compared to tumors developing earlier in life. In the study by Listernick et al.,[167] 15% to 19% of children with NF-1 who underwent CT or MRI had anterior pathway gliomas. Only 20% of these children with gliomas had visual symptoms. Bilateral optic gliomas are more common in patients with NF-1,[168] whereas chiasmal gliomas are more often seen in non-NF-1 patients.[169,170] Patients with NF-1 commonly have optic gliomas that grow cirucumferentially around the nerve. The tumor then breaks through the pia mater and grows within the subarachnoid space to compress the optic nerve. In patients without NF-1, optic gliomas usually grow intraneurally to cause expansion within the optic nerve.[171]

Table 4.3. Diagnostic criteria for neurofibromatosis type I

Diagnosis of neurofibromatosis type I (NF-1) requires two or more of the following features:

- Six or more café-au-lait spots with diameters greater than 0.5 mm before puberty or 1.5 cm after puberty
- Two or more neurofibromas or a single plexiform neurofibroma
- Freckling in the axillary oringuinal regions
- Optic pathway tumor
- Lisch nodules (iris hamartomas)
- Dysplasia of the sphenoid bone or dysplasia/thinning of the long bone cortex
- A first-degree relative diagnosed with NF-1

Adapted from NIH Consensus Development Conference Statement.[172]

Symptoms and Signs

Although the symptoms and signs of anterior visual pathway gliomas primarily depend on the location of the tumor, children with optic gliomas are asymptomatic and their tumor is diagnosed upon neuroimaging for screening of neurofibromatosis or other unrelated reasons.[167,173] The prevalence of radiographically identified optic nerve gliomas in children with NF-1 is approximately 15% in referral centers.[174] Visual loss in at least one eye occurs in 62% of children with NF-1 when the tumor involves the postchiasmal structures and 32% when the lesion involves the chiasm and/or optic nerves.[174,175] Visual loss in the better eye is less likely regardless of the association with NF-1 or the extent of the tumor.[176] In a study by Balcer et al.,[175] 28% of children with NF-1 and gliomas developed visual loss more than 1 year after diagnosis. Most children with NF-1 who had poor vision had their visual loss at the time of diagnosis.[168,175] In a recent series of 54 patients by Thiagalingam et al.,[166] optic pathway gliomas presented in older children between 7 and 15 years of age; 17 of the 56 children were diagnosed after 6 years of age, 22 had tumor progression within 1 year of diagnosis, and 6 showed progression after 1 year.

Visual acuity ranges is variable in which more than half may present with 20/300 or worse.[164] Seventy-five percent or more of patients may

have a relative afferent pupillary defect.[177] Proptosis is a common sign in patients with intraorbital optic gliomas, especially in children.[178,179] Gradual visual loss may be attributed to enlargement of optic gliomas from neoplastic growth, arachnoidal hyperplasia, and gradual cyst degeneration with accumulation of mucopolysaccharide material; all may contribute to separation of longitudinal axon bundles and nerve fiber compression. Rapid visual loss might occur with cystic degeneration or hemorrhage. Vision may occasionally be spared despite extensive proliferation and compression because some nerve fibers may survive for long periods of time; it was observed that visual acuity did not correlate with tumor growth.[164,180] Hoyt et al.[181] described two patients with radiologic evidence of tumor enlargement who maintained stable vision over an 8-year interval. Four additional patients had progressive visual loss despite radiologic demonstration of stability in tumor size after radiotherapy. Spontaneous visual improvement or decrease in tumor size might occur by resorption of mucinous material or variations in hydration.[181]

Visual field defects are common in patients with anterior visual pathway gliomas regardless of tumor location. Central and cecocentral scotomas, arcuate defects, altitudinal defects, and peripheral constriction all reflect injury of optic nerve fiber bundles.[182] If the glioma extends into the chiasm, then junctional scotomas and bitemporal hemianopsias may be observed.

On funduscopic examination, optic atrophy may be seen in two-thirds of patients and optic disc edema in one-third of patients, according to data from 383 patients.[164] Optic disc edema has been observed in 48% of patients with intraorbital optic gliomas[164] and in 22% of those with chiasmal tumors.[164] Optociliary shunt vessels, which are commonly seen in patients with optic nerve meningiomas, occur much less often in patients with optic gliomas. Retinal vascular occlusion,[183] venous stasis retinopathy with iris neovascular glaucoma,[184] or anterior segment ischemia[185] are rarely associated with orbital gliomas.

Ophthalmoplegia is less common in optic gliomas, occurring in 27% of patients with intraorbital tumors and 21% with chiasmal gliomas.[164] Gliomas expanding into the orbital apex may compress the extraocular muscles or ocular motor nerves.

Patients with chiasmal gliomas may also be asymptomatic,[168,173] but the symptomatic ones usually present with bilateral visual loss that does not correlate with tumor size. Because the tumor may affect a combination of optic nerve, optic tract, and chiasm, visual field defects may include central scotomas and bitemporal hemianopias with superimposed homonymous hemianopsias.[186] Optic atrophy may reflect more anterior optic pathway injury, whereas optic disc edema may suggest obstructive hydrocephalus or extensive tumor invasion of the optic nerve.

In contrast to optic gliomas, proptosis is less common with chiasmal gliomas and intracranial symptoms and signs are more prevalent. Based on data from155 patients, about 28% of patients with chiasmal glioma presented with headache.[164] Seizures occurred in 13% of patients with chiasmal tumor involving the midbrain.[187] According to a study by De Sousa et al.,[188] 47% of patients with intracranial gliomas had increased CSF protein. Elevated CSF pressure was present in 85% of patients with chiasmal gliomas in a study of 13 patients by Borit and Richardson.[189]

Similar to optic gliomas, ophthalmoplegias in patients with chiasmal gliomas may be the result of exophytic tumor expansion compressing ocular motor nerves; increased intracranial pressure may also cause a sixth nerve palsy.[164]

Nystagmus was observed in 23% of patients based on data from 264 patients.[164] Nystagmus may suggest intracranial extension of gliomas, especially in infants who have rapid vertical or horizontal pendular oscillations of small amplitude associated with head movements that may mimic the features of spasmus nutans (a benign, spontaneously remitting disorder consisting of asymmetric nystagmus, head nodding, and anomalous head positioning.[190]

Hypothalamic invasion by exophytic gliomas may cause hypopituitarism. This diencephalic syndrome is most often seen in affected children who appear emaciated despite normal food intake and linear growth.[191] Up to 50% to

70% of affected children under 10 years of age may present with precocious puberty, growth failure, diabetes insipidus, and obesity.[192]

Neuroimaging

On high-resolution CT, an optic nerve glioma appears as a well-demarcated fusiform enlargement of the optic nerve[193] and increased tortuosity of the nerve, representing elongation of the optic nerve from secondary axial growth and downward deflection.[194] The tumor is isodense with the brain and enhances variably with contrast. Optic nerve gliomas often have less enhancement than optic nerve sheath meningiomas. Localized low-density areas in the central aspects of the tumor are thought to represent cystic degeneration with accumulation of mucin.[195] The perineural pattern of growth leads to a diffuse enlargement of the optic nerve and appears on CT as a low-density thickened dura surrounding a compressed optic nerve, which is seen as a thin central core of higher density. Calcification is rarely seen and was noted in 14% of cases by Hoyt et al.[180]

CT scan of a chiasmal glioma usually reveals a well-circumscribed enlargement of the optic chiasm or a round, globular suprasellar mass of variable size.[196] Tubular enlargement of the intracranial optic nerves or optic tracts may occasionally be seen on CT. Similar to optic gliomas, chiasmal gliomas variably enhance, and may have regions of lower density, possibly representing cystic degeneration. In contrast to optic gliomas, calcification is more commonly seen in chiasmal gliomas.

MRI offers greater resolution and sensitivity in visualization of anterior visual pathway gliomas. These tumors appear isointense or slightly hypointense relative to the brain on T_1-weighted sequences and hyperintense on T_2-weighted sequences (Figure 4.1).[197] Tumor enhancement is also variable. Intracranial growth and extension along the optic tracts are best visualized on postcontrast T_1- and T_2-weighted sequences. Visualization of glioma in the orbital optic nerve requires proton density or fluid-attenuated inversion recovery (FLAIR) sequences. With this MRI technique, the perineural pattern of arachnoidal gliomatosis would appear as solid tissue rather than water, as seen on T_1- and T_2-weighted sequences.[198,199]

FIGURE 4.1. Optic nerve glioma in neurofibromatosis type I. This axial T_1-weighted MRI demonstrates a left optic glioma with mild dilatation of the subarachnoid space surrounding the origin of the right optic nerve.

The following neuroimaging features of anterior visual pathway gliomas are more commonly associated with NF-1: (1) bilateral optic nerve gliomas,[168] (2) circumferential or perineural growth pattern,[198,199] (3) elongation and downward "kinking" of the intraorbital optic nerve,[200] and (4) posterior extension of the optic chiasmal glioma into both optic tracts and often into the lateral geniculate nuclei and temporal lobes.[196] Hyperintense T_2-weighted signal lesions, which are thought to be hamartomas located in the globus pallidus, cerebellum, internal capsule, and brainstem, may also be seen in 75% of patients with NF-1.[201]

Histopathology

Most optic gliomas are benign, WHO (World Health Organization) grade I pilocytic astrocytomas, characterized by proliferating neoplastic astrocytic cells in which some cells may develop

Rosenthal fibers, enlarged eosinophilic processes surrounded by hyalinized connective tissue.[202] Vascular proliferation and atypia are commonly seen.

In neurofibromatosis, orbital gliomas commonly develop proliferation of arachnoid cells that extend from the nerve through the pia mater into the arachnoid and subarachnoid space. This arachnoid hyperplasia causes reactive proliferation of fibrovascular tissue and meningothelial cells along with neoplastic astrocytes.[203] The arachnoid cell proliferation may also extend beyond the tumor to mimic extension and may even histologically mimic optic nerve sheath meningioma.[203]

Perineural, or circumferential, growth of optic gliomas is seen more often in patients with neurofibromatosis. Proliferating astrocytes enlarge the pia-subarachnoid space to form nests of astrocytes and fibrovascular arachnoidal trabeculae, with mucinous and microcystic degeneration.[204] This circumferential growth compresses the optic nerve. Occasionally, tumor may also grow into the optic nerve without the cystic changes.

In contrast, the intraneural growth pattern of optic gliomas is predominantly seen in patient without neurofibromatosis.[204] The optic nerve is enlarged by expansion of fibrovascular trabeculae by astrocytic proliferation. Cystic degeneration is rare. The enlargement of the tumor in the optic nerve also obliterates the subarachnoid space.[204]

Growth of optic gliomas is often unpredictable and often decreases or halts after reaching a plateau.[203] Proliferation of neoplastic cells, reactive arachnoidal proliferation, and accumulation of extracellular, periodic acid–Schiff (PAS)-positive mucoid substance secreted by astrocytes all lead to gradual enlargement of the tumor.[203] Sudden enlargement can lead to cystic degeneration or intralesional hemorrhage.[205] Eventually, compression from the tumor leads to demyelination, a disruption of the nerve fibers that results in visual loss.[206]

Course and Prognosis

Most untreated gliomas of the anterior visual pathways are slow-growing tumors associated with good long-term survival and good vision.[164] In a review of more than 300 patients from published case series, only 21% of those with untreated or partially resected optic gliomas had recurrence or progression during a mean follow-up period of 10 years.[189] Of 62 patients with unilateral optic gliomas who were either untreated or underwent partial resection, only 12 (19%) developed tumor growth during a mean follow-up period of 7 years.[207] The estimated mortality rate during a mean follow-up period of 10 years was 5%.[207] Most recurrences occurred during the first few years of follow-up. Growth and recurrence of these tumors is followed by a period of stabilization after reaching a plateau. Despite the benign course of optic gliomas, intraparenchymal and leptomeningeal metastases have been documented in some rare cases.[208,209]

Compared to patients with optic gliomas, those with optic chiasmal gliomas have a worse prognosis for survival. The overall mortality rate is determined by the presence or absence of intraparenchymal extension of the tumor. In a study by Miller et al.,[178] gliomas limited to the optic chiasm were associated with a better prognosis for survival than those involving the hypothalamus or third ventricle. In a review of more than 300 patients from published case series by Dutton,[164] the 10-year mortality rate of patients with untreated or partially resected gliomas limited to the optic chiasm was about 17%. The 11-year mortality rate of patients with similar tumors that extended into the hypothalamus or third ventricle was approximately 52%.

The prognosis for survival and rates of recurrence are also influenced by the presence or absence of neurofibromatosis. Most studies show that the presence of NF-1 improves the overall prognosis.[168,187] The results from these series may have been biased by case ascertainment. Optic gliomas are more prevalent in patients with NF-1, and these tumors are associated with a better prognosis. More optic gliomas are reported in asymptomatic NF-1 patients because they undergo routine neuroimaging screening compared to those without NF-1 who are not screened. On the contrary, the presence of NF-1 may pose an increased risk of

developing other NF-1-related central nervous system tumors that can contribute to an overall poor prognosis of survival. In a study of 28 patients with optic chiasmal gliomas,[200] 2 of the 9 patients with NF-1 died as a result of their chiasmal gliomas and the remainder died of complications related to their additional tumors.

Occasionally, spontaneous visual improvement[210] and regression of tumor mass[211] may be observed in patients with anterior visual pathway gliomas. Sudden unpredictable changes in tumor size are thought to be related to acute cystic degeneration, regression of vascular engorgement, and/or intraparenchymal hemorrhage.[211]

Management

In patients with NF-1, ophthalmologic monitoring for optic pathway gliomas is recommended every 3 months after diagnosis, every 6 months at 18 months, and then yearly thereafter. MRI of the brain is recommended about every 6 months for the first 2 years and then yearly thereafter.[212] Although previous studies have documented a mean age at presentation of optic pathway gliomas of around 4 years,[167,212,213] 17 of 54 patients with NF-1 were diagnosed with optic pathway gliomas after age 6.[166] The late-onset tumors in this study were more likely to progress following diagnosis than their counterparts, which presented early in life. Eighty-eight percent of these tumors displayed evidence of ophthalmologic progression, and 50% exhibited radiographic growth.[214] This study suggests that monitoring children with NF-1 up to at least 17 years of age may be necessary to diagnose later-onset optic pathway gliomas.[214]

The management of optic gliomas is controversial. The natural history of these tumors is unclear at this time, as incidences of visual loss, hydrocephalus, and other clinical features vary dramatically among studies. Assessment of treatment efficacy is confounded by unpredictable growth of these tumors. Several studies have shown spontaneous tumor regression after radiographically documented tumor regression.[215,216]

Surgery. There are no studies to support the efficacy of surgical resection of optic gliomas to prevent extension into the chiasm. Biopsy of lesions confined to the visual pathways is not necessary in patients with NF-1. Optic nerve gliomas may even spontaneously regress, as reported in at least 36 patients with or without NF-1. For patients with NF-1 who have hypothalamic extension of the optic glioma, biopsy is controversial because of the risk of further visual loss and hypothalamic dysfunction.[217] For patients with hypothalamic lesions without NF-1, however, biopsy may be reasonable because the risk for malignancy is higher in these patients. Surgical resection of chiasmal/hypothalamic gliomas also remains uncertain. In the series by Wisoff et al.,[218] 10 of 16 patients experienced no further growth of the tumor after surgery at a mean follow-up period of 27 months. Three infants died of tumor recurrence. None of the patients had postoperative decrease in vision or diabetes insipidus. Postoperative hypopituitarism was not reported.

Other relative indications for surgical intervention are primarily for alleviating ocular complications. Surgical resection of a blind, painful eye may offer symptomatic relief for the patient. Ophthalmic plastic surgical procedures would be considered appropriate to reduce proptosis because of cosmetic reasons and/or severe corneal exposure injury.[218]

Although the clinical and radiologic features of optic gliomas are sufficiently characteristic to obviate the need for a biopsy, some patients have large exophytic tumors that may mimic other suprasellar tumors of childhood, such as germinoma or craniopharyngioma.[163] It may be unclear in such cases whether the tumor is intrinsically associated with the optic chiasm or whether it is a suprasellar/hypothalamic lesion extending into the chiasm. Limited excisional biopsy of an exophytic component is not likely to cause further visual loss. No evidence supports that partial resection of these tumors is associated with any significant improvement over observation in terms of rate of recurrence.[219] In patients with infiltrative tumors of the optic chiasm, diagnostic biopsy can injure the anterior visual pathway and cause further visual loss.

Up to 40% of patients who have chiasmal gliomas with large exophytic masses develop or present with hydrocephalus.[162,187] Intraventricular shunt placement is recommended. Although metastatic seeding of the peritoneum following shunt placement rarely occurs, it is not a contraindication.[220,221]

Ascites is a rare complication following placement of a ventriculoperitoneal shunt. In the study by West et al.,[222] each of three children had a shunt for chiasmal glioma complicated by hydrocephalus and developed ascites without malignant cells. The ascites resolved after their shunt was revised to a ventriculoatrial system.

Radiation Therapy. For chiasmatic-hypothalamic gliomas, 80% of patients treated with radiation therapy at 4500 cGy to 5500 cGy experienced stabilization or tumor shrinkage as seen on radiologic studies.[223] The efficacy of radiation therapy on visual outcome and tumor progression is uncertain. In studies by Hoyt and Baghdassarian[181] and Glaser et al.[217] visual outcome was not correlated with radiation therapy in 20 patients. No difference was noted in the disease-free survival rate between the patients who had radiation therapy and those who did not. Even tumor shrinkage on CT scan was not correlated with clinical progression in 16 patients after radiation therapy.[196]

The cognitive and endocrinological side effects of radiation therapy occur most often in children less than 5 years of age when chiasmal gliomas are usually diagnosed.[224] Other complications of radiation include malignancies in patients with NF-1, moyamoya disease, and aneurysms.[225,226] In the study by Tao et al.,[227] long-term follow-up of 29 children with irradiated chiasmal gliomas reported a 10-year survival of 89%. Tumor shrinkage was noted years after radiation. Vision improved in 24%, worsened in 17%, remained stable in 48%, and was not evaluated in 10%. As a complication of radiation therapy, cognitive impairment was found in 71% and hypopituitarism in 72%.

Chemotherapy. No evidence supports the use of chemotherapy in gliomas confined to the optic nerve.[228] Less than 10% of all diencephalic gliomas in patients with NF-1 will require treatment on the basis of progressive visual loss or radiographic enlargement.[228]

Because radiation therapy is not an effective long-term treatment modality for all patients, especially in young children who experience cognitive and endocrinological complications, chemotherapy is a useful alternative for those who have progressive tumors. The combination of carboplatin and vincristine has been shown to be less toxic than radiation and more efficacious than other chemotherapeutic combinations. In a prospective study by Packer[228] in which patients with recurrent or progressive low-grade gliomas received carboplatin and vincristine, 56% of patients with progressive, newly diagnosed lesions had an initial radiographic response, including complete tumor shrinkage. Progression-free survival, as measured radiographically, was about 74% for children less than 5 years of age, and about 39% for children greater than 5 years of age.[228] Therefore, the combination of carboplatin and vincristine is considered, at this time, the preferred treatment for progressive chiasmal or hypothalamic gliomas.

Malignant Anterior Visual Pathway Gliomas

Epidemiology

Malignant anterior visual pathway gliomas often occur in adults with onset at approximately 50 years of age.[164] Men are more commonly affected than women in an approximate ratio of 2:1.[229–231] In contrast to the benign anterior visual pathway gliomas, these malignant tumors are not associated with NF-1.

Symptoms and Signs

Bilateral and asymmetric visual loss is rapidly progressive over an average of 8.7 weeks.[164] It is commonly associated with retro-orbital pain. These visual symptoms can mimic acute optic neuritis.[164] Based upon a meta-analysis of previous case series of patients with malignant optic gliomas,[164] the levels of initial visual acuity of

the more affected eye included the following: 5% had normal visual acuity; 24% had 20/30 to 20/100; 14% had 20/200 to 20/400; 38% had counting fingers to light perception; and 19% had no light perception. The final visual acuity of the more affected eye revealed that 14% had hand motion to light perception and 86% had no light perception. As the tumor extended into the optic chiasm in the early stages, visual loss started in the fellow eye within 5 to 6 weeks and then progressed to blindness.[164]

In the same meta-analysis of previous case series, 94% of the patients had visual field defects. These field defects included any combination of the following: (1) central, arcuate, or altitudinal scotomas if the optic nerve is affected; or (2) bitemporal hemianopias and junctional scotomas, if the optic chiasm is involved.[164]

The optic disc may appear normal in the early stages. As the tumor infiltrates the optic nerve, the disc may become hyperemic and edematous, often with central retinal artery or vein occlusion.[229,231] If the tumor remains in the more posterior aspects of the anterior visual pathway, the disc usually becomes pale without edema. If the tumor extends intracranially, then papilledema from increased intracranial pressure may be seen. In the same meta-analysis of previous case series of patients with malignant optic gliomas, normal optic discs were observed in 25%, disc edema in 43%, optic atrophy in 31%, proptosis in 23%, and ophthalmoplegia in 19%.[164] The expansive effects of the tumor is thought to cause compression on individual cranial nerve palsies or cause mechanical limitation on the movement of the orbit itself. Convergence and other gaze abnormalities are rare.[232]

Malignant gliomas commonly involve the temporal lobes, hypothalamus, and third ventricle to cause seizures, encephalopathy, hemiparesis, and hypothalamic dysfunction. These neurological signs occurred in 35% of patients in the meta-analysis of previous case series.[164]

Neuroimaging

The CT and MRI findings are nonspecific. These malignant tumors often cause enlargement of the chiasm and at least one contiguous optic nerve that enhances after administration of contrast.[233–236] The optic chiasm is affected in nearly all cases, either initially or later as the tumor grows.[164] In the later stages of tumor growth, contiguous infiltration of the anterior visual pathways and exophytic extension from the optic chiasm into the adjacent temporal lobes and hypothalamus/third ventricle may be seen (Table 4.4).

Table 4.4. Frequency of locations of malignant optic gliomas based on a meta-analysis of 31 previously reported patients in the literature

Site of malignant optic gliomas	Frequency (%)
Chiasm and orbital optic nerve	22.6
Chiasm and optic tracts	48.4
Chiasm and hypothalamus	54.8
Chiasm and third ventricle	25.8
Chiasm and basal ganglia	12.9
Chiasm and temporal lobe	19.4

In some patients, multiple sites were involved. Adapted from Dutton.[164]

Based on the radiologic presentation of infiltration of the optic chiasm and other anterior visual pathways, the differential diagnosis of an adult malignant optic glioma would include malignancies, such as lymphoma; infections, such as fungi; and inflammatory disorders, such as sarcoidosis. If the tumor extends into the sellar areas, craniopharyngiomas or malignant pituitary adenomas could be considered.[164]

Pathology

Malignant anterior visual pathway gliomas are characterized as having cellular pleomorphism, numerous mitotic figures, necrosis, and hemorrhage, as seen in anaplastic astrocytomas and glioblastoma multiforme.[229,231,237] Neoplastic cells envelop the optic nerve beneath the pia mater, causing impairment of capillary perfusion, progressive vascular occlusion, and demyelination. Tumor usually spreads below the pia mater along the visual pathways or directly within the substance of the brain to other locations.[229]

Prognosis and Treatment

Malignant optic gliomas cause rapidly deteriorating vision and death within a year in middle-aged men.[229] In a review of 39 reported cases of adult malignant optic glioma by Dario et al.,[237] no statistically significant difference between the survival of patients with only optic involvement and patients with extraoptic involvement was observed. Patients treated with radiation therapy had more favorable survival curves, with a median of 5.5 months, compared to those who were not treated, with a median survival of 3 months. No statistically significant difference was seen in those who received radiation therapy and chemotherapy (median survival, 6 months) and those who did not (median survival, 3 months). Although complete resection of the tumor is not feasible, biopsy of the optic nerve with poorest vision or partial resection of the tumor is usually possible. No statistically significant difference was seen in patients who underwent biopsy of the tumor versus partial resection of the tumor.

Ganglioglioma of the Optic Nerve

Gangliogliomas are composed of mature ganglion cells and mature glial cells that usually grow in the floor of the third ventricle, but may rarely arise within the optic chiasm or intracranial portions of the optic nerves. Gangliogliomas have been reported to infiltrate one or both optic nerves.[238] Vision worsened gradually or suddenly. Lu et al.[239] described a 38-year-old man who developed acute right visual loss with right orbital pain and headaches. MRI of the orbits with contrast revealed an enhancing fusiform dilation of the optic nerve.

On histopathology, gangliogliomas have neoplastic astrocytic proliferation. The glial and neuronal components are well differentiated to the degree that they may mimic pleomorphic fibrillary astrocytomas.[240]

Most gangliogliomas have a natural course similar to that of low-grade astrocytomas and have a good prognosis. If chiasmatic infiltration is present, the survival rate may be slightly lower. Some tumors may have malignant features often occurring in the glial component of the tumor, and metastases may occur.[240]

Secondary Tumors Infiltrating the Optic Nerve

Leptomeningeal Metastases to the Optic Nerve

Meningeal metastasis can infiltrate the optic nerve to cause visual loss.[241] Malignant cells invade the subarachnoid space of the optic nerve with minimal invasion of the optic nerve parenchyma. In some instances, the infiltrative process becomes compressive as the malignant cells grow and expand into the subarachnoid space around the optic nerve. Approximately 30% to 40% of patients with carcinomatous meningitis develop visual loss,[242,243] whereas other studies have found 15% of cases affecting the optic nerves.[244]

Symptoms and Signs

Visual loss in patients with meningeal carcinomatosis commonly occurs after the diagnosis of the primary lesion (lung or breast) has been established. The visual loss may be an isolated finding[245] or may occur with other signs of chronic meningitis.[246] Patients with carcinomatous infiltrative optic neuropathy often present with painless acute or subacute visual loss in one or both eyes. Blindness may even occur within several days.

An afferent pupillary defect, decreased color vision, and visual field defects, such as a central scotoma or nerve fiber bundle defect, may be the initial signs of an infiltrative optic neuropathy. The optic disc usually appears normal at the onset of visual loss. Only after about 6 to 8 weeks does the optic disc show atrophy.[245,246]

Diagnostic Testing

On MRI of the brain with gadolinium, enlargement and enhancement of the orbital and canalicular segments of the optic nerve may be seen. Dural metastases appear as curvilinear contrast-enhancement patterns beneath the inner table of the skull. In contrast, leptomeningeal tumor appears as contrast-enhanced areas that follow gyral convolutions and may also be seen as nodular deposits on the leptomeninges. The diagnosis of meningeal carcinomatosis also

requires CSF cytology; approximately 20 mL or more CSF is often needed to detect malignant cells.[247]

Management

Aggressive therapy with intrathecal chemotherapeutic agents, such as methotrexate, can improve symptomatology in some patients with leptomeningeal metastases, and may even occasionally prolong their median survival period for 8 months.[247] If bulky meningeal metastases are associated with leptomeningeal ones, then local radiation therapy can be added.[247]

Other Metastases to the Optic Disc

In addition to metastases by CSF circulation within the subarachnoid space, tumor may spread to the optic nerve by the adjacent choroid or retina, by the vascular supply to the optic nerve, or by orbital metastases invading intraocularly.[249] Isolated metastases to the optic nerve are extremely rare and occur in 1.3% with histologically proven carcinoma metastatic to the eye and orbit[250] and in 4% with intraocular metastases referred to a tertiary cancer center.[251] Bilateral optic nerve metastases occurs in approximately 18% of patients.[252] Breast and lung carcinomas are the most common metastatic tumors to the optic nerve and uvea. In a study of 29 cases of isolated optic nerve metastasis by Arnold et al.,[253] the primary cancers consisted of 27% breast cancer (4 cases), 27% lung cancer (4 cases), 27% stomach cancer (4 cases), 20% sarcoma (3 cases), and 6% pancreas (1 case). Other types of cancers that have been reported to spread to the optic nerve include prostatic, esophageal, uterine, ovarian, vaginal, hepatic, renal, adrenal, thyroid, and lip carcinomas. Melanomas from the skin have also been reported to metastasize to the optic nerve and optic nerve sheath.

Symptoms and Signs

Visual loss usually progresses over several months. The optic disc is swollen and may have a yellow-white mass of tumor cells.[254] Vitreous tumor cells and hyperemia of uninvolved nerve can also be seen. Compression of venous outflow by the mass of tumor cells may cause retinal venous engorgement and central retinal vein obstruction. If the mass becomes necrotic, then hemorrhage into the optic nerve can occur. Associated choroidal metastases appear as yellow subretinal lesions with a serous detachment of the sensory retina in about 75% of cases.[249]

The differential diagnosis of optic disc metastasis includes primary optic nerve tumors, such as astrocytoma, melanocytoma, and capillary hemangioma; optic nerve granulomas, including sarcoid and juvenile xanthogranuloma; and optic nerve macroaneurysm. Metastasis involving the optic nerve posterior to the lamina cribrosa may mimic retrobulbar neuritis. When metastases extend into the optic nerve posteriorly into the lamina cribosa, the disc may appear normal, mildly hyperemic, or pale, mimicking retrobulbar optic neuritis. The optic disc may also be swollen from increased intracranial pressure from central nervous system (CNS) metastases.[249]

Diagnostic Testing

On fluorescein angiography, the optic disc tumor may be hypofluorescent in the early phases of the study. Leakage of dye occurs in the hyperemic areas of the optic disc. If retinal venous flow is compressed by the tumor, then a delay in venous filling may be seen.[249]

If the diagnosis is uncertain and the patient has no prior history of cancer, then a systemic workup is needed to search for the primary lesion and to exclude other possible etiologies. Neuroimaging with CT, MRI, and ultrasonography may be needed to delineate the intraocular lesion. Lumbar puncture may be necessary to evaluate for any intracranial involvement. Cytology of vitreous or CSF may be required to obtain a histological diagnosis.[249]

Management

Treatment options include observation, radiation therapy, chemotherapy, and enucleation. Observation may be indicated in patients with good visual acuity, especially those who are improving on chemotherapy. External-beam

radiation may be appropriate if vision is impaired. In adults, about 30 Gy to 35 Gy can be given in divided doses over 3 to 4 weeks. For patients with metastatic optic disc tumors with good visual acuity, chemotherapy to control the tumor growth is recommended. If visual acuity is decreased, external-beam radiation may be needed. Secondary optic atrophy may be a complication of radiation therapy. Enucleation would be reserved for those patients with a blind and painful eye.[250]

Prognosis

The prognosis of patients with metastases to the optic nerve is poor. The mean survival of patients with metastatic carcinoma was 9 months after onset of ocular symptoms.[250] The prognosis for survival is likely influenced by the course of the primary malignancy. In a series of 300 patients with ocular metastases, the mean survival of patients with breast carcinoma was 18 months compared with 8 months for patients with lung carcinoma and 5 months for patients with cutaneous melanoma.[250]

Lymphomatous Infiltration of the Optic Nerve

Epidemiology

Infiltration of the optic nerve occurs in 0.5% of patients with non-Hodgkin's lymphoma (NHL).[255] Infiltration of the optic nerve in Hodgkin's disease is even less common. In both NHL and Hodgkin's lymphoma, the infiltration of optic nerves arises from extension of CNS tumor. In primary CNS lymphoma (PCNSL), the incidence of ocular involvement is as high as 20% to 25% at the time of diagnosis. The true incidence of isolated ocular lymphoma is difficult to ascertain because a significant proportion of patients are not accurately diagnosed until they present with subsequent CNS disease. Nevertheless, ocular lymphoma with or without CNS disease affects up to 500 patients per year and is a very rare condition.[256] The average age of onset for isolated ocular lymphoma is in the late fifties to sixties. Women are affected twice as frequently as men.

Symptoms and Signs

Visual symptoms usually present after the diagnosis of lymphoma, but visual loss may occasionally be the initial presenting sign.[257, 258] The location and extent of the lymphoma determines whether the visual loss is slowly progressive[259] or acute.[260] In patients with ocular lymphoma as part of the spectrum of PCNSL or in isolation, the visual symptoms are identical to those of idiopathic vitreitis or uveitis. A lymphomatous infiltrative optic neuropathy can even present in patients thought to be in clinical remission. The most common presentation are floaters, which may enlarge in size to gradually obscure vision. Blurry vision and scotomas are also occasionally present. Bilateral involvement occurs in more than 80% of patients. Those who appear to have unilateral symptoms at onset often have bilateral disease on examination or develop it during the course of their illness. About 50% of patients with ocular lymphoma have no visual symptoms when cells and flare are seen on slit lamp examination. Further funduscopic exam often reveals subretinal deposits of lymphoma and even retinal detachment.[261]

Diagnostic Testing

On cytological evaluation of a vitrectomy specimen, the presence of malignant lymphocytes establishes the diagnosis.[262] Most of these cells are B-cell tumors that stain with B-cell immunohistochemistry markers. Although some reactive T cells are seen, flow cytometry or molecular analysis of the vitreous specimen can confirm the diagnosis and rule out an inflammatory reaction, as seen in idiopathic vitritis.[262] Further testing for elevated levels of interleukin-10 (IL-10), interleukin-6 (IL-6), and interleukin-12 (IL-12) may provide supportive evidence, in addition to cytological results, of ocular lymphoma. Vitreous IL-10 is elevated in ocular lymphoma, but not in idiopathic vitritis, which is associated with elevated levels of IL-6 and IL-12. Monitoring of the levels of IL-10 may also be helpful in measuring therapeutic response in patients with ocular lymphoma.[263]

Neuroimaging

Infiltration of the optic nerve by lymphoma is seen as an enlarged high-density enhancing lesion on CT scan. On MRI, the infiltrated optic nerve can be seen as an enhancing lesion that is iso-, hyper-, or hypointense on T_1-weighted imaging and hyperintense on T_2-weighted imaging.[260]

Management

Prior use of corticosteroids can be cytotoxic to malignant lymphocytes and may cause transient remission of the ocular lymphoma, which often recurs when corticosteroids are discontinued for weeks to sometimes months. Most patients become refractory to repeated courses of corticosteroids.[256]

When the CNS is involved, survival without treatment is very limited such that most patients survive for only a few weeks. Radiotherapy, corticosteroids, and vitrectomy can induce remission but do not substantially improve long-term survival.[256]

Leukemic Infiltration of the Optic Nerve

Epidemiology

Based on a study by Allen and Straatsma,[264] half the patients who died of leukemia had ocular involvement. The acute form of leukemias affected the eye four times more often than the chronic form. About 90% of cases with optic nerve involvement occur in patients with the acute forms of leukemia.[264,265] By the time the optic nerve head is infiltrated by leukemic cells, the disease is often active in the bone marrow.[265]

Symptoms and Signs

In contrast to the good visual function observed with other types of optic disc edema, this infiltrative-related disc edema is associated with decreased visual acuity, variable visual field defects, and a relative afferent pupillary defect unless the infiltration is bilateral and symmetric. It is often associated with peripapillary and peripheral retinal hemorrhages.[265] Leukemic cells may also infiltrate the optic disc to form a circumscribed, white elevated lesion associated with yellow deposits and peripapillary hemorrhage.[266] Subretinal fluid may also develop secondary to retinal pigment epithelial damage.[267–269] The visual acuity in such patients is relatively preserved, unless the infiltration or associated edema and hemorrhage extends into the macula.[270] In addition, optic disc swelling and neovascularization may occur as a local phenomenon in the setting of diffuse retinopathy of acute leukemia.[271]

The differential diagnosis of optic disc edema in patients with leukemia includes leukemic infiltration of the CNS with secondary increased intracranial pressure, pseudotumor cerebri related to prolonged corticosteroid use, tumor infiltration of the optic nerve resulting in ischemic papillitis, and perivascular tumor infiltration leading to venous engorgement.[266]

Although most infiltrative optic neuropathies are attributed to acute leukemias, chronic leukemias may cause more slowly progressive and less severe visual loss. The optic disc edema is similar to that seen in patients with acute leukemias but without the retinal changes.[272]

Similar to lymphomatous infiltrative optic neuropathies, MRI demonstrates abnormal enhancement in optic nerves infiltrated by leukemia. This lesion is iso-, hyper-, or hypointense on T_1-weighted imaging and hyperintense on T_2-weighted imaging.[263]

Pathology

Leukemic infiltration of the optic nerve via the pial septae causes optic disc swelling. This edematous appearance may mimic papilledema caused by increased intracranial pressure. The leukemic cell infiltration proximal to the optic nerve just posterior to the lamina cribrosa contributes to the disruption of axoplasmic flow and compression of nerve fibers to cause disc edema.[266–268] Hemorrhagic necrosis and tumor cells can be seen in the edematous disc and in the retrolaminar interneuronal spaces.[272]

Management

Early, aggressive radiation therapy is the most effective treatment of incipient optic nerve head infiltration by leukemia. In a study by

Rosenthal et al.,[265] four eyes with leukemic infiltration were treated with 2000 rads external-beam radiation over a 1- to 2-week period. Visual function rapidly returned to normal or near normal, and the disc edema resolved. On histopathological examination of these eyes, tumor cells were absent in the prelamnar and retrolaminar regions of the optic nerve.

Myelomatous and Other Lymphoreticular Tumor Infiltration into the Optic Nerve

Multiple myeloma, lymphomatoid granulomatosis, and Langerhans' cell histiocytosis may cause an infiltrative and/or compressive optic neuropathy.[273] Bourdette and Rosenberg[274] described a patient with polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes (POEMS) who developed an infiltrative orbitopathy and had blind spot enlargement that improved after corticosteroid treatment. Another report[275] described a patient who developed an optic neuropathy and a chiasmal syndrome resulting from infiltration from reactive lymphohistiocytosis secondary to phenytoin use. Vision improved after treatment with corticosteroids and radiation therapy.[275,276]

Inflammatory Infiltrative Optic Neuropathies

Sarcoidosis

Epidemiology

Sarcoidosis is a relatively common disorder, occurring as often as 82 cases per 10,000 persons in the United States. It affects blacks more severely, and they have twice the frequency of ocular involvement as Caucasians. Most symptomatic patients are between 20 and 40 years of age.

Sarcoidosis is the most common inflammatory etiology of infiltrative optic neuropathies. About 1% to 5% of patients with systemic sarcoidosis have optic nerve involvement.[277] Optic nerve dysfunction occurs in patients with neurosarcoidosis. Coexisting uveitis may obscure optic nerve involvement. In a study of 68 patients with neurosarcoidosis reported by Zajicek et al.,[278] the optic nerve or chiasm was affected in 38%. Of these patients, 69% had unilateral optic nerve involvement and 31% had bilateral involvement.

Symptoms and Signs

Sarcoidosis may cause an ischemic optic neuropathy, papilledema from a compressive process, or an anterior or retrobulbar optic neuritis from a granulomatous infiltrative process.[279] Visual acuity loss is associated with decreased color vision, visual field defect, and a relative afferent pupillary defect, unless the involvement is bilateral and symmetric. An isolated infiltrative optic neuropathy can manifest initially, or it may occur with other signs of hypothalamic dysfunction, hypothalamic hypopituitarism, or both.[279] Sarcoidosis also causes perioptic neuritis.

On funduscopic examination, the optic disc is usually elevated diffusely or sectorially with nodules. This yellow-white cauliflower-like formation over the disc can also be clearly seen on ultrasonography. Surface disc blood vessels appear dilated, and peripapillary hemorrhages may be seen. Pressure from the lesion can cause a branch retinal vein obstruction. Noncaseating granulomas usually infiltrate the optic disc unilaterally. Although it is not often associated with anterior uveitis, posterior uveitis and retinal phlebitis occur in 80% of cases.[280] Sarcoidosis may affect the posterior retrobulbar or intracanalicular portion of the optic nerve to cause gradual visual loss and a normal optic disc that gradually becomes pale. Visual acuity ranges from 20/20 to hand motions.[281]

Although sarcoid-related disc edema in the setting of progressive visual loss commonly occurs in association with ocular inflammation,[282] it may be difficult to distinguish it from compressive optic neuropathies, such as optic nerve sheath meningiomas. A retrobulbar presentation of sarcoidosis can also mimic optic neuritis. Atypical features of peripapillary hemorrhages or the persistent dependence of visual function on steroids may help differentiate sarcoid optic neuropathy.[282]

Diagnostic Testing

The diagnosis is usually confirmed by other systemic clinical, radiographic, and laboratory evidence of sarcoidosis. Laboratory tests supporting the diagnosis of sarcoidosis include an elevated angiotensin-converting enzyme (ACE) level and histological evidence of sarcoidosis by biopsy. Sensitivity of serum ACE is 84% and the specificity is 95%. The combined use of ACE levels and gallium scans can also increase specificity.[283] Furthermore, abnormal uptake on gallium scanning may represent areas suitable for biopsy. Affected conjunctival or lacrimal glands may also be biopsied. Epithelioid and giant cell infiltration forming noncaseating granulomas can be seen on biopsy of the optic nerve.[284] On CSF analysis, the CSF protein is elevated in 73% of patients with neurosarcoidosis; the lymphocytic count is elevated; CSF glucose levels are usually normal; CSF oligoclonal bands are present in 55%; and CSF ACE levels are elevated in up to 50% of patients.[278] The optic neuropathy may be subclinical in some cases. In patients with neurosarcoidosis, 48% (23 of 50) patients had visual evoked potential (VEP) abnormalities, but none had visual symptoms. Fluorescein angiography shows early hypofluorescence, then hyperfluorescence from leakage of disc blood vessels within the lesion.[277] On MRI, the enlargement and contrast enhancement of the orbital portion of the optic nerve are nonspecific for sarcoidosis. The posterior orbital portion of the optic nerve often reveals enlargement and contrast enhancement on MRI and CT, and the optic foramen is often enlarged. Sarcoidosis may extend even more posteriorly to infiltrate the basal meninges, the intracranial portion of the optic nerve, and the optic chiasm.[278]

Pathology

Histologically, the optic nerve can be infiltrated by noncaseating granulomas consisting of epithelioid and inflammatory foreign-body giant cells. Asteroids, star-shaped acidophilic bodies, and Schaumann bodies, ovoid, basophilic, birefringent calcium oxalate crystals, may be found within or surrounded by the epithelioid or giant cells.[284]

Management

Corticosteroids are the main treatment of sarcoidosis. Oral prednisone at 40 mg to 80 mg daily is recommended for neurosarcoidosis. Higher pulse treatments are required when patients are unresponsive. Steroid-sparing agents, such as cyclosporine, azathioprine, methotrexate, and cyclophosphamide, may be required for long-term immunosuppression.[285]

Idiopathic Perioptic Neuritis

Epidemiology

Perioptic neuritis affects older patients with a range from 24 to 60 years of age, in which 36% are older than 50 years of age, compared to optic neuritis, in which 15% are older than 50 years of age. The exact prevalence of this rare disorder is not known at this time.[286,287]

Symptoms and Signs

Perioptic neuritis may manifest as orbital or ocular pain, decreased vision, and a normal or swollen optic disc that may mimic acute optic neuritis. It is usually an isolated, idiopathic disorder that involves inflammation of the optic nerve sheath.[286] In contrast to optic neuritis that affects central vision, paracentral or arcuate defects are more commonly seen in perioptic neuritis. Although vision often spontaneously recovers in optic neuritis, visual loss often progresses over weeks in perioptic neuritis.[287]

Diagnostic Testing

If vitreous cells or retinal infiltrates are seen, then screening for sarcoidosis, syphilis, Lyme disease, and tuberculosis is necessary on serum and CSF. CSF results for these disorders would reveal a normal opening pressure and a mild pleocytosis.

In perioptic neuritis, MRI enhancement of the optic nerve with occasional streaks of enhancement of the orbital fat with or without extraocular muscle enhancement can be seen.[287] Enhancement of the lesion on T_1-fat-suppressed imaging is nonspecific but is also highly suggestive of this disorder.[288] In optic neuritis, MRI

enhancement of the optic nerve with or without white matter lesions is usually observed.

Pathology

On histopathology, lymphocytic infiltration and fibrotic thickening of the optic nerve sheath with foci of degenerating collagen can be seen.[289] Granulomatous inflammation in the nerve sheath, vasculitis in the nerve sheath, and optic nerve demyelination or infarction have also been reported.[289,290]

Management

In contrast to patients with optic neuritis, those with perioptic neuritis often experience recurrence of visual loss and are not predisposed to developing a demyelinating disease. In contrast to the corticosteroid treatment protocol of the ONTT for patients with optic neuritis, oral prednisone is given at 80 mg daily.[287] Other steroid-sparing agents may need to be administered on a long-term basis to prevent irreversible visual loss and to induce remission in some patients.

Infectious Infiltrative Optic Neuropathies

Tuberculosis

Epidemiology

Mycobacterium tuberculosis is an obligate aerobe and facultative intracellular parasite that can survive in mononuclear phagocytes and is able to invade local lymph nodes to spread by hematogenous routes. Since 1985, the incidence of tuberculosis has increased in association with the acquired immunodeficiency syndrome (AIDS), affecting adults 25 to 40 years of age and during a later peak about 70 years of age.

Symptoms and Signs

As a granulomatous inflammatory disease, tuberculosis causes a papillitis more often than it infiltrates the optic nerve.[291] Lana-Peixoto et al.[292] reported an intrinsic tuberculoma of the left intracranial optic nerve on autopsy of a 1.5-year-old child with tuberculous meningitis and disseminated military tuberculosis. In a report by Iraci et al.,[293] a 25-year old man with severe visual loss, diabetes insipidus, and sexual impotence from tuberculous meningitis had a tuberculoma encasing and growing into the anterior optic pathways. Biopsy confirmed the diagnosis, and antituberculous treatment led to recovery of vision in one eye.

Neuroimaging

MRI of the brain often reveals basilar meningeal enhancement and communicating or noncommunicating hydrocephalus. Tuberculomas in the brain parenchyma and optic pathways appear as multiple ring-enhancing nodular lesions that represent caseating granulomas. Old tuberculomas often calcify.[294]

The primary diagnostic and screening test for tuberculosis is the tuberculin skin test with purified protein derivative (PPD) and is positive in 50% to 80% of cases. CSF analysis reveals a lymphocytic predominance with elevated protein and decreased glucose. CSF acid-fast bacillus smear is positive in about one-fourth of cases. CSF culture is positive in about one-third of cases. CSF polymerase chain reaction (PCR) testing is not sensitive but is specific.[295]

Pathology

Small white tubercles are scattered mainly over the basal meninges. The tuberculomas can both encase and invade the optic nerve to cause an infiltrative and compressive optic neuropathy. They consist of a central core of caseation surrounded by epithelioid cells, giant cells, lymphocytes, plasma cells, and connective tissue. An exudate, consisting of fibrin, lymphocytes, plasma cells, and other monocytes, also obliterates the pontine and interpenduncular cisterns and can spread to the optic chiasm and cranial nerves via the subarachnoid space.[296]

Management

The treatment of tuberculosis requires early treatment. If resistance to isoniazid and rifampin

is suspected, then pyrazinamide and ethambutol should be added. Pyridoxine is added to prevent peripheral neuropathy from isoniazid neurotoxicity. Prednisone or dexamethasone for edema from tuberculous meningitis improves morbidity and mortality. An infectious disease specialist should also be consulted for management.[296]

Cryptococcosis

Epidemiology

Cryptococcus neoformans is an opportunistic fungus that often infects those with underlying illness or immunodeficiency, such as AIDS. Since the development of antiretroviral therapy and fluconazole prophylaxis, the incidence of cryptococcal meningitis has decreased. Without these medications, cryptococcal meningitis is one of the most common CNS complications of immunocompromised patients in the developing world.[297] It affects adults more commonly than children.

Symptoms and Signs

Visual loss may be either acute and severe, occurring in less than 24 h, or gradually progressive. Patients may begin with mild visual loss and then progress to severe visual impairment over weeks to months. In a study by Rex et al.,[298] the predictive factors for either acute or gradual visual loss were the presence of papilledema, an elevated CSF opening pressure, and a positive CSF India ink preparation. Medications that reduced intracranial pressure most consistently improved vision in patients who had gradually progressive visual loss. Corticosteroids did not significantly improve visual outcome.

In a study of 80 human immunodeficiency virus (HIV) seropositive patients with cryptococcal infection,[299] 32.5% (26 of 80) patients developed papilledema. Visual loss and sixth nerve palsy occurred in 9%, and optic atrophy was observed in 2.5% of patients. Among the 62 patients treated with oral conazoles, optic nerve-related visual loss was less frequent compared to the 18 patients treated with amphotericin B or a combination of amphotericin B and conazoles. Although direct invasion of intraocular structures by *Cryptococcal neoformans* was a rare complication in this study, direct invasion of the optic nerve by the organism has been demonstrated so far in at least 40 patients.[298]

Pathology

Cryptoccocal organisms can infiltrate the optic nerve to cause visual loss over several days. In a pathological study of a patient with AIDS who developed cryptococcal meningitis,[300] focal necrosis of the right intracanalicular optic nerve and the left intraorbital optic nerve adjacent to the optic canal was thought to have caused sudden bilateral visual loss. The meninges surrounding the optic nerve, chiasm, and tracts were filled with cryptococcal organisms. Blood vessels supplying the optic chiasm were normal. Generalized cerebral edema and vacuolization of periventricular white matter were also observed. The visual loss from cryptococcosis can also occur more gradually over a period of months.[301–304] Cryptococcal organisms in the optic nerve sheath have been shown to be present at the time of sheath fenestration. Despite the visual loss that can occur from papilledema in cryptococcal meningitis, it was concluded that the poor visual outcome after this procedure could have been related to the direct invasion of cryptoccocal organisms into the optic nerve.[301–304]

Diagnostic Testing

MRI of the brain reveals basilar meningeal enhancement and gelatinous-appearing pseudocysts extending along enlarged perivascular spaces, especially in the basal ganglia.[305]

CSF analysis reveals a lymphocytic predominance, but polymorphonuclear cells may be present; protein is usually 50 to 1000 mg/dL, and glucose is often less than 40 mg/dL. A definite diagnosis of cryptococcal meningitis is established by a positive CSF culture for *C. neoformans*, a positive CSF India ink stain, or a reactive CSF cryptococcal antigen test.[306]

Management

For acute therapy of cryptoccal meningitis, intravenous amphotericin B with oral flucyto-

sine for at least 2 weeks is followed by oral fluconazole to complete a 10-week course until the CSF is sterile. After this 10-week course, if CSF is still not sterile, maintenance therapy with a lower dose of fluconazole should be started. If the patient has AIDS, then antiretroviral therapy needs to be started. An infectious disease specialist should also be consulted for management.[307]

Other Infectious Etiologies

Although toxoplasmosis and cytomegalovirus commonly cause a posterior uveitis, rare evidence shows that these organisms can primarily affect the optic nerve. In a retrospective study of 13 patients with toxoplasmosis affecting the optic nerve head,[308] patients with primary toxoplasmic involvement of the optic nerve head who were treated had a final visual acuity of 20/25 or better. Visual field defects were arcuate or altitudinal. This anterior toxoplasmic optic neuropathy is difficult to diagnose because there is typically no associated vitritis or chorioretinitis. Cytomegalovirus infiltration of the optic nerve is an unusual manifestation. Only one case report documents the presence of cytomegalovirus invasion of the optic nerve head in a 51-year-old immunocompromised patient suffering from lymphoma. No lymphoma cells were seen in the optic nerve.[309]

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5
Traumatic Optic Neuropathies

Jane W. Chan

Traumatic Optic Neuropathy as a Complication of Head Injury

Epidemiology

Traumatic optic neuropathy may be a result of severe head trauma or may be associated with little or no evidence of head injury. Traumatic optic neuropathy occurs in approximately 0.5% to 5% of closed head injuries[1] and in 2.5% of patients with maxillofacial trauma and midface fractures.[2] Loss of consciousness is associated with traumatic optic neuropathy in 40% to 70% of cases.[3,4] In closed head injuries, the site of injury causing blindness is often the forehead or supraorbital ridge, less commonly the temporal region. Patients from 20 to 40 years of age represent the major trauma population who experience traumatic optic neuropathy.[5]

The prevalence of severe initial visual loss ranges from about 43% to 56%. Visual loss may present with no light perception to 20/20 with an associated visual field defect. More severe visual loss is usually associated with optic canal fracture. In some studies, 43% (6/14)[6,7] to 56% (13/23)[8] of patients presented with light perception or no light perception (NLP) following traumatic optic neuropathy.

Deceleration injury directed to the ipsilateral forehead or to the midface region from motor vehicle and bicycle accidents is the most common cause of traumatic optic neuropathy in 17% to 63% of cases.[9] The second most common cause of traumatic optic neuropathy is motorcycle accidents followed by falls in as many as 50% of cases.[9] Other situations that may cause traumatic optic neuropathy include assault, gunshot wounds, falling objects, skateboarding, and even very minor head injuries. Iatrogenic injury may occur during endoscopic sinus surgery and orbital surgery.[9]

Basic Anatomy of the Optic Nerve

To better understand the location and mechanisms of optic nerve injury, the anatomic relationships are reviewed.

Optic Nerve Head

The axons of the retinal ganglion cells converge on the posterior pole of the globe at the optic disc. The intraocular portion of the optic nerve is approximately 1 mm long and is the shortest portion of the nerve. It can be divided into prelaminar and laminar segments. In the prelaminar portion, the optic disc, which is oval shaped and approximately 1.5 mm horizontally × 1.75 mm vertically, consists of unmyelinated axons of the retinal ganglion cells, astrocytes, capillary-associated cells, and fibroblasts. The central retinal artery and vein traverse centrally from the disc. These millions of axons emerge from the globe as fascicles and pass through the lamina cribrosa, 200 to 300 fenestrations through the choroids, and sclera in the laminar portion of the optic nerve head.[10]

The size of the scleral canal and the angle of exit of the canal from the eye may cause variations in the appearance of the optic disc.

A larger scleral canal leads to a larger physiological cup size. A smaller scleral canal causes a small or absent physiological cup and gives the appearance of a crowded optic nerve head.[10]

The ophthalmic artery arises from the ophthalmic branch of the internal carotid artery. It passes anteriorly through the optic canal alongside the optic nerve, which is covered with dura. In the orbit, the ophthalmic artery gives rise to the central retinal artery, which enters the optic nerve sheath approximately 10 mm behind the globe and extends anteriorly to emerge from the center of the optic disc. The central retinal artery does not directly supply blood to the optic disc. Much of it is derived from the choroidal feeder vessels, short posterior arteries, and some from the pial arterial network, which all contribute to the circle of Zinn–Haller, a perineural arteriolar anastomosis that encircles the optic nerve head. The retrolaminar portion of the optic nerve is supplied by anastomosing branches of the central retinal artery and the pial arteries. The laminar and prelaminar portions of the nerve are mainly supplied by branches of the posterior ciliary arteries. Only a small fraction of the blood supply to the optic nerve head comes from choroidal branches of the posterior ciliary arteries that extend to the optic nerve head.[10]

The central retinal vein drains most of the optic nerve head. During chronic compression of the intraorbital optic nerve or after central retinal vein occlusion, optociliary shunt vessels (preexisting anastomosis between superficial disc veins and choroidal veins) may enlarge and shunt venous blood from the retina to the choroids. Eventually, it drains into the vortex veins leading to the superior and inferior ophthalmic veins.[10]

Orbital Optic Nerve

From the posterior aspect of the globe, the orbital segment of the optic nerve extends to the orbital apex. It is approximately 25 mm long and has a sinuous course that allows free movement of the globe and protects the nerve from injury when there is orbital proptosis.[1] The width of the orbital optic nerve is about 3 mm to 4 mm in diameter, twice as wide, mainly because of the myelin produced by oligodendrocytes and its encasement with meninges. Myelination of the axons of retinal ganglion cells extends from the point where they exit the globe to the point where they synapse in the lateral geniculate nucleus. The myelinated optic nerve is encased with all three layers of the meninges (the dura, arachnoid, and pia mater). The outermost layer is the dura, which is composed of collagen and is continuous with the sclera. At the orbital apex, the dura fuses with the periosteum and with the annulus of Zinn. Underneath the dura is the arachnoid. Arachnoid trabeculae connect this layer with the dura and the underlying pia mater, where capillaries traverse as they enter into the substance of the optic nerve. The subarachnoid space, filled with cerebrospinal fluid (CSF), is continuous with the intracranial portion.[10]

As the optic nerve passes posteriorly toward the optic canal, it is surrounded by orbital fascia, fat, nerves, and vessels. Most of the blood supply to the orbital optic nerve derives from capillaries from the surrounding pial plexus. In the posterior orbit, the optic nerve is crossed superolaterally by the nasociliary branch of the trigeminal nerve, ophthalmic artery, superior ophthalmic vein, and superior division of the oculomotor nerve. The superior rectus, levator palpebrae muscles, trochlear nerve, and frontal branches of the trigeminal nerve are located superior to the optic nerve in the roof of the orbit. Inferior to the optic nerve at the floor of the orbit lie the inferior and medial recti muscles and the inferior division of the oculomotor nerve. Between the optic nerve and the lateral wall of the orbit are the lateral rectus muscle and abducens nerve. Between the lateral rectus muscle and the optic nerve is the ciliary ganglion, parasympathetic postganglionic neurons innervating the constrictor pupillae and ciliary muscles.[10]

Regarding the blood supply of the optic nerve, the anterior orbital optic nerve is surrounded by four posterior ciliary arteries that are branches of the ophthalmic artery. In the middle of the orbit, the ophthalmic artery traverses inferolaterally to the optic nerve until it crosses under (or occasionally over) it. In 6%

of cases, the ophthalmic artery can lie medially to the optic nerve as they both reach the orbital apex and pass through the annulus of Zinn, a tendon from the origin of insertion of the four recti muscles.[11] The medial location of the ophthalmic artery is predisposed to injury during a trans-sinus approach for optic nerve decompression.[11]

Intracanalicular Optic Nerve

The optic nerve, ophthalmic artery, and sympathetic fibers from the carotid plexus all enter the optic foramen of the optic canal in the apex of the orbital roof. The ophthalmic artery enters the optic canal inferior and lateral to the optic nerve. The length of the optic canal is about 10 mm. It is formed by the two lesser wings of the sphenoid bone. Its thinner medial wall separates the optic nerve from the sphenoid and posterior ethmoid sinuses. In about 4% of patients the optic nerve may have areas covered only by the nerve sheath and sinus mucosa, without any bony covering between the intracanalicular optic nerve and the adjacent paranasal sinus. These sinuses may eventually enlarge into the optic canals producing pneumosinus dilatans. This finding is often seen with an adjacent optic nerve sheath meningioma.[10]

Because the dura of the optic nerve is fused with the periosteum of the optic canal, impact forces that deform bone may be more easily transmitted to the intracanalicular portion of the optic nerve. The intracanalicular optic nerve is also susceptible to injury under the fixed edge of the falciform dural fold at the near edge of the optic canal. The tightly fixed optic nerve within the optic canal is also predisposed to compression from small lesions, arising within the optic canal or at either of its openings, that may be difficult to visualize on thin-section computed tomography (CT) or magnetic resonance imaging (MRI) scanning.[10]

Intracranial Optic Nerve

The intracranial optic nerve is covered by a firm fold of dura as it exits the optic canal. The distance between the two optic nerves at this point is about 13 mm, and they extend posteriorly, superiorly, and medially to join at the optic chiasm. The length of the intracranial optic nerve varies from 3 mm to as long as 16 mm, but is usually about 10 mm. If the intracranial optic nerve is shorter than about 12 mm, the optic chiasm is prefixed, in which it is located more anteriorly and superiorly to the sella turcica. If the intracranial optic nerve is longer than 18 mm, the optic chiasm is postfixed, in which it is located more posteriorly to the dorsum sellae. The variation in the length of the optic nerve affects the types of visual field defects caused by tumor in the suprasellar region.[10]

Dorsal to the optic nerve is the olfactory tract at the ventral surface of the frontal lobes. Ventral to the optic nerve are the anterior cerebral and anterior communicating arteries. The internal carotid artery from the cavernous sinus may sometimes emerge laterally to the optic nerve. The optic nerve is also adjacent to the internal carotid artery where it bifurcates into the anterior cerebral and middle cerebral arteries and to the proximal portion of the posterior communicating artery. The intracranial optic nerve is supplied by the ophthalmic artery from the internal carotid artery. These anatomic relationships predispose the optic nerve to be injured by traumatic aneurysms of the internal carotid, ophthalmic, and anterior cerebral arteries.[10]

Localization of Direct Optic Nerve Injuries from Head Trauma

Direct injury to the optic nerve needs to be distinguished from indirect injury. Direct injury arises from penetrating trauma, such as from orbital fractures associated with midfacial fractures. The most common optic nerve injuries involve posterior indirect injuries, followed by chiasmal, and direct injuries. Direct traumatic optic neuropathy is less common because the laxity of the intraorbital optic nerve allows for both absorption and deflection of the penetrating object. The resilience of the dura to penetration also offers further protection.

If an object penetrates into the orbit, the optic nerve may be directly injured by complete or partial transaction of the nerve, contusion of the nerve, or by compression from hemorrhage or foreign-body impingement.[12] Optic nerve

transection occurs as a complication of midfacial trauma and orbital fracture. Visual loss is NLP caused by transection of the optic nerve, perhaps from a bony fragment seen on CT scan.

If orbital hemorrhage is present, an orbital compartment syndrome may occur. An enlarged optic nerve sheath may also be seen on CT. Orbital hemorrhage may be diffuse or localized in the orbit. It is often accompanied by proptosis and ophthalmoplegia. Increased orbital pressure causes injury to the optic nerve, which may be decreased by elevating the head and administering acetazolamide to lower intraocular pressure. If not, lateral canthotomy and drainage of the orbital hemorrhage may be necessary.[12]

Orbital emphysema can also occur in the setting of paranasal sinus injury. Thin fractures of the bone lining the orbital wall may produce a ball-valve effect so that air accumulates in the orbit to cause proptosis and compression of the optic nerve. Drainage of air by insertion of a needle into the retro-orbital space may resolve this condition.[12]

Optic nerve avulsion is often caused by sudden rotation or anterior displacement of the globe with a finger or object to result in optic nerve injury at the lamina cribosa.[12] Funduscopic findings are commonly seen and include peripapillary vitreous hemorrhage, partial or complete optic nerve head avulsion, optic disc swelling, venous congestion, central retinal artery nonperfusion, and retinal edema. In partial and complete avulsion of the optic nerve head, a ring of hemorrhage is formed around the optic disc. The site of avulsion is seen as a dark crescentic area over the disc. If injury occurs at the orbital optic nerve anterior to the point at which the central retinal artery enters and the central retinal vein exits, arterial and venous obstruction and disc swelling may be seen.

Optic nerve swelling without retinal changes can also occur from hemorrhages in the optic nerve sheath posterior to the origin of the central retinal vessels. Prompt treatment of an optic nerve sheath hematoma may lead to visual recovery. An expanded nerve sheath causing proptosis and a central retinal artery or vein occlusion could indicate the presence of an optic nerve sheath hematoma, especially in the setting of a progressive optic neuropathy. Drainage by sheath fenestration usually restores vision.[13,14]

Localization of Indirect Optic Nerve Injuries from Head Injury

The most common optic nerve injuries involve posterior indirect injuries, followed by chiasmal, and direct injuries (Table 5.1).[15]

Posterior indirect is the most common type of traumatic optic neuropathy and is usually a result of a frontal or midfacial trauma that also may be trivial. The intracranial portion of the nerve is relatively fixed within the bony canal. The orbital bone transfers force from the forehead and brow to the orbital apex.[16,17] The intracanalicular portion of the optic nerve is the most common site of indirect optic nerve injury.[18] Visual loss is usually immediate, and less often delayed or progressive, with variable visual field defects associated with an afferent papillary defect and/or dyschromatopsia. Often no ophthalmoscopic signs of injury are seen initially. Injury to the distal optic nerve in the orbit, optic canal, or intracranial cavity usually leads to disc atrophy and pallor after 3 to 5 weeks. If head trauma with loss of consciousness produces increased intracranial pressure, papilledema may be seen. Optic canal fracture on CT often does not correlate with the severity of the optic neuropathy. It is also imperative to distinguish a preexisting optic neuropathy, which can be observed as optic atrophy in a patient with acute head trauma.[9]

The intracranial portion of the optic nerve is least likely to have traumatic damage. Chiasmal injury is uncommon and is usually the result of severe closed head injury or an abrupt traction on the globe. The tethering of the optic nerve within the optic canal may prevent transmission of force to the chiasm. According to a review of 18 cases of autoenucleation,[19,20] 33% of the optic nerve transections occurred at the anterior chiasm, whereas 55% of them occurred at the orbital apex. This review and other studies[21,22] suggest that strong and abrupt tractional forces on the globe are required to cause tears in the

Table 5.1. Types of traumatic optic neuropathy from head injury (adapted from Lessell[15])

Type	Pathogenesis	Clinical findings	Management
Direct	Penetrating object causing direct injury to the optic nerve by complete or partial transection of nerve or contusion of nerve; hemorrhage or foreign body compressing the optic nerve.	Initial variable level of vision that often worsens. Orbital hemorrhage may cause orbital compartment syndrome. Enlarged optic nerve sheath may be seen on CT scan.	Removal of foreign body impinging on optic nerve. Lateral canthotomy and cantholysis; drainage of subperiosteal hematoma if present. Optic nerve sheath fenestration if nerve sheath hematoma or edema is seen on CT scan, and if hematoma is confirmed to be subdural on oblique view on MRI scan.
Anterior indirect	Sudden rotation of anterior displacement of globe with object causing injury to the anterior segment of the optic nerve, often at the lamina cribrosa. Rare type of traumatic optic neuropathy.	Prepapillary vitreous hemorrhage. Partial or complete optic nerve head avulsion. Papilledema, venous congestion, central retinal artery occlusion, retinal edema.	Treatment for central retinal artery occlusion, if present. Look for occult rupture of the globe or extraocular muscle avulsion.
Posterior indirect	Frontal or midfacial trauma or trauma that may appear trivial causing indirect optic nerve injury. Most common type of traumatic optic neuropathy.	No ophthalmoscopic signs of injury. Afferent pupillary defect and/or dyschromatopsia. Immediate visual loss is common. Delayed or progressive visual loss occurs in a few cases. Loss of consciousness and midfacial fractures are common. Variable visual field defects. Optic canal fracture on CT does not correlate with severity of optic neuropathy.	(See Management section.)
Chiasmal	Severe closed head injuries or an abrupt traction on the globe may cause chiasmal injury.	Variable visual field defects. Central visual acuity may be normal. Anosmia, diabetes insipidus, or other endocrinopathies; skull base fractures and other neurological deficits may be present.	No treatment for optic nerve injury. Neurosurgical consultation may be needed for associated intracranial injuries.

optic nerve with chiasmal injury. Clinical findings may include normal central visual acuity, variable visual field defects, such as bitemporal hemianopsia and defects from unilateral lesions of von Willebrand's knee. Anosmia, diabetes insipidus, or other endocrinological disorders, fractures of the skull base, cerebrospinal leakage, meningitis, thalamic injury, and other neurological deficits may also be seen. No treatment is yet available.[19]

Diagnostic Tests

Traumatic optic neuropathy is a clinical diagnosis. It usually occurs after head trauma with or without loss of consciousness. Decreased best

corrected visual acuity and an RAPD, without other ocular pathology that could account for the visual loss, would support the diagnosis of traumatic optic neuropathy affecting the posterior orbital, intracanalicular, or intracranial portion of the optic nerve. These patients usually have 20/400 or less in the affected eye.[15] More subtle optic nerve injury, which is thought to occur in less than 10% of cases,[4] may present as delayed visual loss.

Examination of the ocular adnexa is important to identify orbital rim fractures and periorbital swelling, which can mimic proptosis. Resistance to retropulsion of the globe and increased intraocular pressure measured by tonometry can help detect retro-orbital hemorrhage. Retraction of the swollen eyelids is needed to look for evidence of penetrating ocular injury. Blunt injury to the iris can cause hyphema, angle recession, and even lens dislocation.[15]

On funduscopy, a ring of hemorrhage at the site of injury is indicative of partial or complete avulsion of the optic nerve head.[23] Injury between the globe and where the central retinal vessels enter the optic nerve can cause venous obstruction and traumatic anterior ischemic optic neuropathy.[13,24] Hemorrhage in the optic nerve sheath posterior to the origin of the central retinal vessels may produce only optic disc swelling.[25] Papilledema from increased intracranial pressure may even be superimposed on traumatic optic neuropathy.[26] Decreased visual acuity with an afferent papillary defect without intraocular pathology is usually indicative of intracanalicular or intracranial optic nerve injury.

If the patient is unconscious or if the RAPD is absent in bilateral cases, visual evoked potentials (VEP) may help in confirming the suspicion of traumatic optic neuropathy, especially in comatose patients. In unilateral traumatic optic neuropathy, flash VEP amplitudes that are at least 50% of the normal eye are critical for a good visual outcome.[27] An absent VEP response indicates that visual loss is complete, and recovery of vision is unlikely.[28] An absent electroretinogram (ERG) is associated with a poor potential for visual recovery.[29]

Localization of injury by visual field testing is limited. There is no pathognomonic visual field loss diagnostic of optic nerve injury. Altitudinal visual field defects, central, paracentral, and centrocecal scotomas, and generalized field constriction have been reported.[3,30–32] Humphrey visual field testing or confrontational testing at the bedside is useful in documenting degree of visual recovery. Optical coherence tomography (OCT) is able to assess and monitor axonal loss after traumatic optic neuropathy.[33] Based upon earlier work by Lundstrom and Frisen,[34] serial fundus photography showed that trauma to the intracranial optic nerve caused gradual disappearance of the retinal nerve fiber layer (RNFL) during weeks 4 to 8. Similar RNFL changes can be seen with the use of OCT.

Early transient increase followed by progressive loss of the retinal nerve fiber layer in traumatic optic neuropathy can be documented by the GDx NFL scanning laser polarimeter nerve fiber analyzer (Laser Diagnostic Technologies, San Diego, CA, USA). In a study by Miyahara et al.,[35] the early increase in RNFL represented transient edema of the nerve fibers. Nerve fiber atrophy was completed by day 90 following the injury and was correlated with enlargement of the optic disc. A scanning laser polarimeter nerve fiber analyzer may be used to quantitate the severity of optic nerve damage and the effectiveness of therapy in traumatic optic neuropathy.

Neuroimaging may also help in localizing the site of optic nerve injury. CT scan with 1.5-mm axial sections allows good reformation along any axis and allows sufficient resolution to image optic nerve position orbital hematoma, orbital edema, intrasheath hematoma, nonorganic foreign bodies, and bony fractures. Optic canal fractures are seen on CT scans in approximately 36% to 67% of cases.[36] The force from trauma is transferred to the sphenoid and then to the optic nerve as it traverses the optic canal.[37] After metallic foreign bodies are ruled out by CT scan, MRI is more sensitive for detecting chiasmal injury and subtle intraneural or intrasheath hemorrhage, distinguishing it from epidural hemorrhage.[4,38] MRI of the orbit may reveal focal edema of the optic nerve or optic nerve sheath enhancement with gadolinium. On T_2-weighted images, the

hyperintense signal from CSF surrounding the injured optic nerve may be absent when compared with the normal nerve. MRI may distinguish intrasheath from intraneural hemorrhage. MRI is also superior to CT in delineating chiasmal injury.[39–41]

Color Doppler imaging may help to differentiate extrinsic optic nerve compression caused by orbital hemorrhage from other causes of optic neuropathy. The B-scan portion of this imaging technique may also help identify optic nerve sheath hematoma.[42,43] The color Doppler portion may help in evaluating perfusion to the optic nerve head.[44,45]

Visual Prognosis

In the natural history of indirect posterior optic nerve injuries, recovery is never complete. Subtle visual field, color vision, and papillary defects persist despite complete recovery of visual acuity by Snellen measurements. Most patients develop optic atrophy. Spontaneous improvement from case series ranged from 20% to 71%.[6,46,47] In Lessell's series,[6] the extent of visual loss did not correlate with the potential for spontaneous recovery. The variation in extent and rate of recovery and response to treatment could be related to the pathogenesis of traumatic optic neuropathy in various clinical circumstances. For direct optic nerve injuries, the possibility of visual recovery is much less, but recovery of vision has occurred in such cases.

In indirect traumatic optic neuropathy, four features were significant in predicting no recovery of visual acuity: (1) the presence of blood in the posterior ethmoidal cells; (2) loss of consciousness associated with traumatic optic neuropathy; (3) absence of recovery after 48 h of corticosteroid treatment; and (4) age of patient over 40 years.[48] Patients who have the foregoing four poor prognostic factors could be considered for optic canal decompression. In this study, 87% of patients who had improved visual outcome experienced visual recovery within 48 h of the initiation of corticosteroid treatment. Another sign of favorable recovery is optic nerve swelling after blunt trauma has been associated with a favorable prognosis for visual recovery. Brodsky et al.[49] reported three patients who had partial recovery of vision.

Pathology

Based on 174 postmortem examinations by Crompton[18] on patients who died after closed head trauma, optic nerve dural sheath hemorrhages was found in 83% of patients. Interstitial optic nerve hemorrhages occurred in 36% of these patients; two-thirds had the hemorrhage within the optic canal. Tears and ischemic lesions occurred in 44% of patients; in 81%, these involved the intracanalicular optic nerve, and in 54% these affected the intracranial optic nerves.

From a case series of patients who had blunt head trauma, more than 50% of patients who had traumatic optic neuropathy were found to have sphenoid bone fractures on CT scan. Laser interferometry studies done by Anderson et al.[17] showed that forces applied to the frontal bone during a deceleration injury are transmitted to and concentrated in the optic canal. Elastic deformation of the sphenoid bone allows transfer of the force into the intracanalicular portion of the optic nerve. The firm attachment of the dural sheath to the optic nerve in the optic canal is thought to predispose it to shearing forces, resulting in tearing of axons and vessels that leads to contusion necrosis. The development and location of a fracture depends upon the elasticity of the bone, in that thicker bone is more inelastic and more likely to fracture. Direct injury to the optic nerve from displaced bony fragments in the optic canal is uncommon.

Shearing forces from blunt head trauma can displace the intracranial optic nerve upward against the falciform dural fold that overlies the intracranial end of the optic canal, resulting in direct or indirect injury. A frontal blow is transmitted posteriorly along the orbital walls to the sphenoid bone and the optic canal. A deceleration injury would allow the globe and the majority of the intraorbital contents to continue forward, whereas the intracanalicular optic nerve would remain immobile because of its tethering at the orbital apex and optic canal. The deceleration would be a shearing force to

the optic nerve. Direct optic nerve injury from partial or complete avulsion from the globe usually does not sever the nerve and often leads to permanent injury to just a portion of the nerve.[17]

Although optic canal decompression is performed based upon the hypothesis that edema inside the bony canal may lead to more swelling and ischemia of the optic nerve, there is not much evidence that optic nerve edema within the optic canal plays a significant role in causing traumatic posterior optic neuropathy. Vascular changes in and around the optic nerve may play a more important role than just the swelling of the nerve itself. Decreased perfusion pressure to the optic nerve within the optic canal during increased intracranial pressure can also decrease blood flow to the optic nerve causing ischemia.[5]

Pathogenesis

Forces from shearing injury cause tears to the microvasculature that are seen as hemorrhage in the optic nerve and its sheaths on pathology. Indirect trauma to the axons may also cause a focal area of impaired axonal transport. This functional separation of the nerve into a proximal and distal segment usually occurs within 6 to 24 h of injury.[50] The distal segment that is separated from the soma undergoes Wallerian degeneration. The proximal segment that is connected with the soma swells to produce a retraction ball. The soma then may undergo apoptosis, as shown in studies of optic nerves after ischemic optic neuropathy, with experimental glaucoma, and after trauma.[51–53]

Apoptosis is programmed cell death involving active cellular processes through final common pathways. Injured retinal ganglion cells release extracellular glutamate that induces excitotoxicity. High glutamate concentrations activate *N*-methyl-D-aspartate (NMDA) receptors that allow entry of excessive calcium into the cell. It has been shown that optic nerve crush leads to an increase in extracellular vitreal glutamate, but the steps by which axotomy induces excitotoxic damage to ganglion cells is still being studied.[54] This abnormally high concentration of calcium leads to inappropriate activation of cascades of proteases, nucleases, and lipases that attack cellular constituents, leading to the generation of highly reactive free radicals. The final stage of apoptosis, execution, occurs through the activation and function of caspases, aspartate-specific cysteine proteins. There are at least 10 homologues of the initially described caspase, interleukin-1-beta-converting enzyme (ICE).[55] The predominant caspase involved in cell death appears to be CPP32 (caspase-3). Caspase inhibitors may be a possible therapeutic target (see Management section).

Intracellular calcium also activates inducible nitric oxide synthase (NOS) to cause increased production of nitric oxide, a highly reactive free radical used for the signaling and regulation of various physiological processes that also induces apoptosis. Free radicals from various sources cause intracellular degeneration and activate the early steps of the apoptotic cascade.[56–59] Retinal ganglion cells do not have NOS.[60] NOS-mediated excitotoxic cell damage relies on the abundant amounts of inducible NOS expressed in reactive astrocytes. In situ hybridization shows intense nitric oxide synthase mRNA signals in the ganglion cell layer and inner nuclear layer, indicative of neuronal NOS proteins being transported through axons into the terminals in the inner nuclear layer. Neuronal NOS appears to play a role in retinal ganglion cell excitotoxicity mediated via the NMDA receptor.[61]

In addition, the excess calcium can also directly cause mitochondrial failure, causing depletion of energy and the generation of more free radicals. Partial ischemia and reperfusion of transiently ischemic areas may generate further oxygen free radicals.[62] The release of these oxygen free radicals leads to peroxidation of lipids in the retinal ganglion cell membrane.[63]

Bradykinin and kallidin initiate the release of arachidonic acid from neurons. Through a series of steps, arachidonic acid is transformed into various types of prostaglandins and oxygen free radicals are released. Peroxidation of lipids in the cell membrane may lead to decreased vascular autoregulation and increasing cellular/tissue edema. This type of edema within the optic canal may then produce a compartment

syndrome causing more ischemia to the optic nerve. Loss of regulation of calcium homeostasis leads to shifting of extracellular calcium to the intracellular space by voltage-gated and receptor-gated calcium channels. The excess intracellular calcium leads to cell death.[63]

Besides ischemia, inflammation contributes to further neural damage. Mediators of inflammation are released to attract polymorphonuclear lymphocytes and macrophages. Within the first 2 days after injury, polymorphonuclear lymphocytes predominate to cause immediate tissue damage. They are then replaced by macrophages by about 7 days after injury. These macrophages are thought to contribute to delayed tissue damage, as in delayed posttraumatic demyelination. Macrophages release glial promoting factors. This astroglial response after spinal cord injury may inhibit axonal regeneration processes. Inhibition of macrophage responses have been shown to decrease reactive gliosis, as shown in spinal cord injury studies.[62,63]

Management

Currently, the use of systemic corticosteroids in traumatic optic neuropathy is accepted as some form of treatment that is better than none at all. The beneficial effects of this medication are extrapolated from those shown in the treatment of acute spinal cord injury in the second National Acute Spinal Cord Injury Study (NASCIS-2).[64] In NASCIS 2,[64] a multicenter, randomized, double-blind, placebo-controlled study in patients with acute spinal cord injury, patients were randomly assigned to receive placebo, naloxone, or methylprednisolone within 12 h of spinal injury. Methylprednisolone was given as an initial dose of 30 mg/kg followed by a continuous infusion of 5.4 mg/kg/h. Compared with placebo, treatment with methylprednisolone within 8 h of injury resulted in a significant improvement in motor and sensory function. These effects of methylprednisolone in the treatment of spinal cord trauma do not seem to extend to the treatment of optic nerve trauma, however. The International Optic Nerve Trauma Study in 1999[65] showed that neither corticosteroid treatment nor optic canal decompression changed the visual outcome of patients with traumatic optic neuropathy. It was clinically reasonable to consider treatment on an individual patient basis. In this prospective observational study, visual outcomes were compared with patients following observation alone, high-dose steroids given within 7 days of the injury, and optic canal decompression with or without corticosteroids and performed within 7 days of the injury. The initial visual acuity of NLP predicted a poor outcome in all groups. No clear benefit was demonstrated for patients undergoing high-dose steroid therapy, or canal decompression surgery compared to observation alone. The 57% improvement of 3 Snellen lines or more in the untreated group suggested that spontaneous visual recovery also played a role in visual outcome. Some studies[66,67] have even shown that methylprednisolone exacerbated axonal loss after optic nerve crush injury in rodent models. In a more recent study by Ohlsson et al.,[68] however, methylprednisolone showed no effect on retinal ganglion cell survival, macrophage activity at the site of injury, axonal degeneration/regeneration, or visual function. These results could explain the lack of efficacy demonstrated in the International Optic Nerve Trauma Study, in which there was no clear benefit for either corticosteroids or optic canal decompression. No randomized, double-blind clinical studies to date provide evidence that methylprednisolone is more effective than observation in the treatment of optic nerve trauma.

Surgical decompression of the optic canal for intracanalicular traumatic optic neuropathy has a limited role in the management of traumatic optic neuropathy. This treatment is based on the hypothesis that swelling in the optic canal may lead to a compartment syndrome. The increasing edema would decrease tissue perfusion to cause more postinjury ischemia to the optic nerve. This procedure is thought to decrease edematous pressure in the optic canal to reverse ischemia and axonal conduction block, which can result in irreversible axonal degeneration.[69,70] In the International Optic Nerve Trauma Study in 1999,[65] no clear benefit was demonstrated for patients who were given high-dose corticosteroids within 7 days of injury

compared to those who underwent optic canal decompression within 7 days of injury with or without corticosteroids. About 57% of the untreated group experienced a spontaneous improvement of visual acuity of 3 lines or more. The initial visual acuity of NLP predicted a poor prognosis. According to a review by McCann and Seiff,[71] 28% of patients with traumatic optic neuropathy have some spontaneous improvement in vision. Based on combined unmatched uncontrolled human studies, vision improves in approximately 50% of patients treated with corticosteroids, 57% of patients treated with optic nerve decompression, and 62% of patients treated with corticosteroids and optic nerve decompression.[71] Most patients with a response to corticosteroids will have improved 1 week after initiating treatment.[72] Of patients treated with corticosteroids who did not improve after 3 weeks of observation, 51% still benefit from surgery.[71,72] The final visual outcome was not correlated with the interval between injury and surgical intervention.[5,71–74] Therefore, optic canal decompression surgery has a limited role in the management of traumatic optic neuropathy, it is appropriate for conscious patients without injuries to the globe who also have progressive visual deterioration.

Management guidelines for direct and indirect traumatic optic neuropathy[15,75–77] should be individualized according to the patient's situation. In the review by Bilyk and Joseph,[12] it is recommended that an eye examination must rule out other etiologies of decreased vision and exclude occult ruptured globe. If a subperiosteal hematoma is present, then a canthotomy and cantholysis should be performed for drainage. If there is no contraindication to corticosteroids and it is within 8 h of injury, then methylprednisolone at 30 mg/kg/h IV is immediately given as a loading dose, and then 4.0 mg/kg/h continuous IV infusion for 24 h, or an additional 15 mg/kg 2 h later and 15 mg/kg every 6 h for up to 72 h. According to most clinicians, if the patient is evaluated beyond 24 h of injury, then no corticosteroids are indicated. High-resolution CT scan of the orbit and sinuses with 1.5-mm axial and coronal sections with bone windows should be performed to include the optic canal and cavernous sinus. If bony fragments are seen to impinge on the intracanalicular optic nerve, or if no fracture or a fracture without obvious impingement is seen on CT scan, then an optic canal decompression should be considered. Visual function needs to be monitored every 2 to 4 h for the first 12 h. If vision improves on high-dose corticosteroids, then an oral prednisone taper is recommended after 72 h of IV steroids. If vision does not improve during the first 12 to 24 h of high dose corticosteroids, then an optic canal decompression can be offered to the patient. Patients who are unconscious and who have injuries to the globe should not undergo surgery. If the optic nerve injury is more than 7 days old, then surgery is also not an option.

According to Sofferman,[78] adequate decompression of the optic canal requires (1) removal of at least 50% of the circumference of the osseous canal; (2) removal of bone along the length of the canal; and (3) total longitudinal incision of the dural sheath including the annulus of Zinn. In cases where visual loss is progressive and delayed with the evolution of an intrasheath hematoma, surgical decompression of the intracanalicular nerve has been proposed.[14,76,77]

There are several possible approaches to the decompression of the optic canal. (1) Goldberg and Steinsapir[79] recommend a transethmoidal/transorbital approach, which allows removal of more than 180° of the bone. Some recent reports have demonstrated that the endoscopic ethmoidectomy technique may offer another surgical option.[80] In a report of 31 patients[81] with indirect traumatic optic neuropathy who received methylprednisolone injections and endoscopic optic nerve decompression, 70% of 23 patients who started treatment before 7 days after injury experienced visual improvement.

Lateral canthotomy and cantholysis are necessary for orbital hemorrhage/edema causing a compressive orbitopathy and optic neuropathy. Orbital CT should then be performed to rule out a subperiosteal hemorrhage or other ocular pathology that could account for the visual loss. If vision does not improve, orbital decompression may need to be considered to allow expansion of orbital soft tissues.[79]

In children and adolescents, traumatic optic neuropathy is caused by mechanisms similar to those that cause it in adults. In a retrospective review of 40 children,[82] treatment did not improve visual outcome. The severity of visual loss and rate and degree of improvement are also similar. The most common causes were motor vehicle accidents (62%) and sports injuries (22%). Trauma was blunt in 78% of cases and penetrating in 22%. Improvement was more likely when vision was 20/200 or better at presentation, regardless of treatment. Patients with NLP acuity at presentation rarely experienced significant visual improvement despite treatment. Severe initial visual loss with baseline NLP and the presence of a fracture in the optic canal on CT scan were poor prognostic signs, predictive of poor visual outcome. Three patients in this series had an improvement of at least 2 Snellen lines from a baseline of NLP after treatment.

New Perspectives in the Protection, Repair, and Restoration of the Injured Optic Nerve

Strategies for neuroprotection, defined as intervention to produce enduring benefits by favorable influencing underlying etiology or pathogenesis and thereby forestalling onset of illness or clinical decline,[83] have been investigated to prevent apoptosis in the management of traumatic optic neuropathy. It has recently been shown that the innate adaptive T-cell-mediated immune response directed against self-antigens located at the site of damage can be neuroprotective after optic nerve or injury. This protective autoimmune response is spontaneously evoked in some individuals, but not strongly enough to significantly affect recovery. By augmenting this response in individuals who spontaneously manifest it and by inducing this autoimmune response in those incapable of manifesting it, optimal neurological functional recovery was attained.[84–86] Protective autoimmunity is defined as a benign autoimmune response that contributes to the maintenance and protection of injured neurons and the promotion of recovery after traumatic injury to the neuron.[84,87] The mechanism of T-cell-mediated neuroprotection is not yet known. Vaccination of rats and mice with the synthetic copolymer Cop-1 after optic nerve crush injury leads to a significantly increased survival rate of retinal ganglion cells.[84,88] Compared to the untreated group, rats treated with antimyelin basic protein T cells had higher visual evoked potentials at days 1, 5, 7, and 15 after crush injury to the optic nerve.[89,90] Vaccination did not induce autoimmune disease based on repeated passive transfer experiments using T cells directed against myelin basic protein itself compared to the nonencephalitogenic cryptic epitope.[91] Similar neuroprotective efficacy was observed with both sets of T cells, suggesting that autoimmune disease was not an inevitable side effect of treatment with T cells that recognize myelin basic protein.

The benefits from T-cell-mediated neuroprotection is manifested by a reduction of secondary degeneration,[92] which may be induced by increased concentrations of glutamate, nitric oxide, or other mediators of toxicity. Augmenting or inducing the body's own mechanism for protective intervention in neural injury allows for more physiological mediated benefit with minimal risk.

NMDA receptor blockers, such as memantine and dizocilpine (MK801), and AMPA and kainite receptor blockers, such as NBQX and DBQX, have been shown to protect retinal ganglion cells after experimental optic nerve injury in animals.[62,63,93,94] To control nitric oxide synthase-mediated damage, *N*-nitro-l-arginase, nipradilol, and aminoguanidine can reduce nitric oxide or inhibit NOS for neuroprotection.[95]

Alpha-2-adrenergic receptors, such as brimonidine, have a neuroprotective effect on the experimentally injured optic nerve when brimonidine is injected intraperitoneally.[96,97]

Caspase inhibitors block apoptosis and may be important therapeutic molecules for the treatment of traumatic optic neuropathy and other neurodegenerative diseases.[98] Intraocular injection of various caspase inhibitors has been shown to salvage up to 34% of retinal ganglion cells from cell death after optic nerve transection.[99]

Because a lack of neurotrophins can lead to apoptosis, supplying the damaged neurons with neurotrophins may promote neuronal survival. These neurotrophins can be delivered directly to the injured neurons, or their genes can be transferred to the neurons by viral vectors. Fibroblast growth factor injected into the spinal cord of adult rats after injury prevents ventral horn neurons from death with improved respiratory function.[100] In experimental optic nerve crush injuries in cats, intravitreal injection of either brain-derived growth factor (BDGF) or glial-derived neurotrophic factor (GDNF) has been shown to increase the survival of retinal ganglion cells.[101–103] Several neurotrophins have been shown to increase glutamate transporter expression in culture and possibly to reduce excitotoxicity. Therefore, both caspase inhibitors and neurotrophins may delay retinal ganglion cell death in the setting of axonal injury.[101–103]

Because of the inherent axonal regeneration inhibitory molecules, such as Nogo, MAG, and OMgp, in the myelin and oligodendrocytes of the central nervous system (CNS), antibodies against these various molecules have allowed the optic nerve to regenerate in animals.[104] Antibodies against central myelin proteins added to crushed optic nerves in mice have resulted in axonal sprouting.[105] Blocking the Rho inhibitory pathway with enzyme C3 in mice has lead to axonal regeneration after transection and reconnection of the optic nerve in vivo.[106] Exogenous growth factors, such as BDNF, neurotrophin-3, and neurotrophin-4, can enhance further axonal repair and regeneration in the optic nerve and spinal cord.[100,107] Optic nerve transection has been shown to also lead to an increased level of GDNF and its receptors as an innate response to injury. Both endogenous as well as exogenous GDNF can support axotomized retinal ganglion cells in neuroprotection and neuroregeneration.[108] Optic nerve regeneration can also be induced by intraocular injection of dibutyryl cAMP. Dibutyryl cAMP has been shown to induce significant axonal regeneration through the crush site of injury of the optic nerve in mice.[109]

Gene therapy is still experimental and may offer limited restoration of vision in injured optic nerves, because this treatment slows the rate of ganglion cell loss after injury and does not prevent a significant proportion of injured cells from dying. A treatment that can stimulate the regeneration of axotomized retinal ganglion cells would be needed.[110]

Furthermore, Schwann cells and fibroblasts isolated from the peripheral nerve can promote retinal ganglion cell survival after optic nerve transection, possibly by secreting neurotrophic factors. In adult rats with transected optic nerves, Schwann cells and fibroblasts from peripheral nerve have been transplanted intravitreally to promote intraretinal axonal sprouting.[111] In a study by Vidal-Sanz et al.,[112] up to 10% of the retinal ganglion cells grew an axon into the peripheral nerve graft connecting the severed optic nerve with the superior colliculus in the rat. Anatomic synapses were demonstrated.

Substances that guide axonal growth towards the target neurons, such as integrins, are inherently present for the appropriate synaptic connections to be established after optic nerve injury. Retinal ganglion cells can navigate their way to synapse correctly to form retinotopic connections, which has been shown histologically in animal models following optic nerve transection and peripheral nerve grafting.[113,114] In a study by Thanos et al.,[115] peripheral nerve grafting between both severed optic nerves and the optic tract allowed axons to reinnervate the major visual targets in the midbrain and thalamus. Restoration of visual function was confirmed by the animal's ability to discriminate spatial patterns and by the presence of visual evoked cortical potentials.

Stem cell implantation offers more hope for the restoration of vision. These cells are pluripotent and differentiate into any neural cell type to integrate with host cells. Stem cells from the retina and the ciliary body of human embryos can be induced to differentiate into retinal ganglion cells.[116] Another possible and still experimental technique is to harvest cells from the host's ciliary body that have the potential to develop into retinal neuronal and glial cells.[117] Stems cells from the ependymal zone of the hippocampus[118] can be placed in the subretinal space to allow engraftment into the retina and

growth of axons toward the host optic nerve. In humans, a sural nerve graft may need to be placed in the opening of the sclera, choroids, and retina on the nasal side of the optic disc with the other end of the graft in contact with the ipsilateral geniculate body.[119]

Gene therapy can help slow the rate of retinal ganglion cell loss after axotomy. Cheng et al.[120] showed that adeno-associated virus-mediated gene transfer to increase the expression of the trkB receptor by retinal ganglion cells to stimulate the receptors with intravitreally delivered BDNF would then increase neuronal survival after optic nerve transection. With this technique, 76% of retinal ganglion cells remained alive at 2 weeks after axotomy, compared to less than 10% of the neurons without treatment. Similar slowing of retinal ganglion cells has been shown with adenoviral delivery of X-chromosome-linked inhibitor of apoptosis (Ad. XIAP) to the optic nerve stump. After adding intravitreal adenovirus encoding glial cell line-derived neurotrophic factor (Ad.GDNF), 47.3% of retinal ganglion cells were rescued from apoptosis 2 weeks after transection.[121] Although these animal models yield promising therapy, the slowing of neuronal death after axonal injury is unlikely to be sufficient for visual function in humans. Treatment that can either prevent a significant proportion of injured neurons from apoptosis or which can stimulate the regeneration of axotomized retinal ganglion cells is needed.

Traumatic Optic Neuropathy as a Complication of Ocular Surgery

Surgical procedures in and around the optic nerve are becoming important causes of direct and indirect optic nerve trauma.

Optic Nerve Injury Related to Periorbital Injections

Anesthetic injections at the orbital apex may cause direct optic nerve injury.[122–125] Katsev et al.[126] recommended that the needle introduced beyond the orbital rim for both intraconal and periconal injections be no longer than 31 mm to avoid damage to the optic nerve. MRI of the orbit often reveals localized edema of the optic nerve or optic nerve sheath enhancement with gadolinium. The hyperintense signal from CSF around the injured optic nerve may be absent on T_2-weighted imaging when compared with the normal nerve. Optic nerve injury has been reported with other procedures with a blunt cannula and in sub-Tenon's injection.[125]

An MRI of the orbits with T_1 fat saturation and gadolinium is recommended for any optic neuropathy occurring within the first 24 h of periocular injection. If findings of needle injury are present, then a trial of high-dose corticosteroids should be considered, although corticosteroids have not been proven to be efficacious. In treatment with corticosteroids, in three of four patients[122–124] only one patient had partial visual recovery.[5–7]

Optic Nerve Injury after Cataract Surgery

Cataract surgery is one of the most common ocular surgeries, and visual loss is a rare complication. Nonarteritic ischemic optic neuropathy (NAION) following uncomplicated cataract surgery with either periocular anesthesia or general anesthesia has been reported.[127–131] In a retrospective study by McCulley et al.,[132] 2 of 5787 patients developed ischemic optic neuropathy within 6 weeks of cataract surgery, but 1 had previous NAION in the other eye 21 months earlier. In another study by McCulley et al.,[133] all 18 cases of NAION in the 17 patients occurred within 6 months of surgery. These data help confirm that intraocular lens surgery is associated with the occurrence of NAION.

Visual loss may present with optic disc edema as an anterior ischemic optic neuropathy or with a normal disc as a posterior ischemic optic neuropathy.[128,129] NAION after cataract surgery may occur within several hours to 4 to 6 weeks postoperatively. It has been shown that if ischemic optic neuropathy occurs in one eye after cataract surgery, the risk of recurrence in the other eye may be as high as 30% to 50% with subsequent surgery.[127,131] It has been postulated that an increase in intraocular pressure during

the postoperative period may contribute to the development of NAION. In a study of 11 patients with NAION after cataract extraction, Hayreh[128] postulated that the typical increase in intraocular pressure after surgery along with a decrease in systemic blood pressure during general anesthesia lead to decreased perfusion of the optic nerve head and ischemia. The type of anesthesia during surgery was not specified in this case series. There are also other studies that document affected patients with normal intraocular pressures in the perioperative period.[127,134]

Most patients experience spontaneous improvement in visual acuity. Corticosteroids have not been shown to be effective. Most clinicians monitor the intraocular pressure in the perioperative period to help prevent the first ischemic event. Because the risk of NAION to the other eye is high, subsequent contralateral cataract extraction is not recommended.[128]

Optic Nerve Injury after Vitrectomy

Ischemic optic neuropathy after vitrectomy to relieve vitreous traction in macular holes is related to surgical manipulation and to local anesthesia. After a pars plana vitrectomy, the cortical vitreous is peeled off the retina, at least around the hole. Aspiration of the cortical vitreous around the optic nerve head may occasionally extend to the equator. This suctioning process of the posterior hyaloid may shear peripapillary axons. Near the nasal edge of the disc, an air–fluid exchange is performed that can cause direct pressure to the optic nerve. At the end of the procedure, the eyes are usually filled with long-acting gas, such as perfluoropropane or sulfur hexafluoride. Patients are then required to position themselves face-down for at least 20 h per day for about 2 weeks. Because the intraocular pressure may rise in the immediate postoperative period to cause optic nerve head ischemia, topical medications or oral acetazolamide are given to patients to help prevent this complication.[135–140]

Postoperatively, patients may develop visual field defects. In a study by Melberg and Thomas,[139] 3 of 157 patients had temporal visual field defects after vitrectomy. In 2 of 3 patients the visual field defects were beyond the central 30° of fixation and could only be detected by Goldmann perimetry. These absolute defects could not be attributed to retinal detachment or schisis. As all patients underwent general anesthesia, injury to the optic nerve was unlikely. It was hypothesized that direct trauma to the optic nerve during aspiration of the air–fluid exchange procedure caused these field defects. In another study,[138] 8 patients experienced visual loss after vitrectomy and all had retrobulbar injections; 7 of 8 patients had fluid–air exchange with long-acting gas; 4 of 8 patients developed afferent pupillary defects, and 4 of 8 developed inferotemporal field defects. Five of 8 had optic disc pallor without associated disc edema. No branch retinal vein or branch retinal artery occlusions occurred. The few retinal detachments did not explain the visual field defects. It was postulated that direct trauma to the optic nerve occurred, either by mechanical pressure from the suction catheter tip during air–fluid exchange or by injury from the needle during retrobulbar injection. Indirect trauma secondary to suction on the posterior hyaloid or shearing of peripapillary axons was another possibility. Although increased intraocular pressure may cause ischemic optic neuropathy, no increase in intraocular pressure was noted during the surgery. In another study, Boldt et al.[135] suggested that direct compression from the gas bubble itself could cause enough pressure to damage the nerve fiber layer. The retina may also have toxic injury from the gas bubble itself. Other studies confirm the common finding of temporal field defects with vitrectomies for macular holes.[136,137] The incidence of inferotemporal or temporal visual field defects ranges from 1.9% to 20.5%. In the study by Paques et al.,[140] 10% of patients had arcuate defects.

Optic Nerve Injury after Trabeculectomy

Visual loss after trabeculectomy is not common. Patients who seem to be at highest risk for significant visual loss after trabeculectomy are those who have advanced glaucoma with preexisting severe visual loss. These high-risk patients often have a field defect that splits fixation or extends within 5° of fixation. Other patients with postoperative hypotony may be

predisposed to ischemic optic neuropathy. In a study of 508 eyes of 440 patients,[141] only 4 cases (less than 1%) of visual loss were observed. These 4 patients had preoperative visual field defects that split fixation, a finding consistent with a study by Kolker.[142] Three of these patients also had postoperative hypotony in which the intraocular pressures ranged from 0 mmHg to 2 mmHg on postoperative day 1. The low pressures persisted for 1 week in 2 eyes and for 1 month in 1 eye. Disc edema was not observed, but another study by Kawasaki and Purvin[143] described 2 patients who developed unilateral optic disc edema after trabeculectomy with intraocular pressures in the low-normal range. Because they did not have severe glaucoma, they did not experience visual field defects. Therefore, intraocular pressures that are too low might predispose to optic nerve injury.

Optic Nerve Injury after Blepharoplasty

Optic nerve injury is uncommon after blepharoplasty. Blindness is estimated at 0.04%.[144] Visual loss is most likely caused by compression of the optic nerve or of the central retinal artery by a retrobulbar hematoma. The visual loss is reversible with prompt treatment. In a report by Kelly and May,[145] a patient developed unilateral blindness from a retrobulbar hemorrhage after lower eyelid blepharoplasty. No blood flow was seen in the retinal arterioles, but after immediate lateral cantholysis and drainage, the patient regained retinal perfusion and recovered normal vision within 72 h. Other similar cases of optic nerve dysfunction secondary to compression by a retrobulbar hematoma after blepharoplasty have been reported with documented abnormal visual evoked potentials and normal electroretinogram.[146,147]

Optic Nerve Injury after Endoscopic Sinus Surgery

PION following intranasal anesthetic injection has been thought to be related to submucosal injection of an anesthetic with epinephrine, causing vasospasm.[148]

Traumatic optic neuropathy can rarely be seen after endoscopic sinus surgery. The lack of orientation to surgical landmarks predisposes the surgeon to this complication.[149] The optic nerve canal indents the lateral wall of the sphenoid sinus, an important surgical landmark. Onodi cells usually cover the sphenoid sinus, but can also surround the optic nerve to cause confusion in surgical anatomy. CT scan cannot reliably identify these cells to help prevent this problem.[150]

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6
Nutritional and Toxic Optic Neuropathies

Jane W. Chan

Nutritional and Toxic Optic Neuropathies

Symptoms

The symptoms and signs of nutritional and toxic optic neuropathies are similar in that they usually present simultaneously and bilaterally. Symptoms are progressive with bilateral symmetric visual loss without pain. Some patients may initially only observe dyschromatopsia, such that certain colors, such as red, are not as bright. Usually only one eye may be involved in the early stages before the other becomes symptomatic. If one eye is severely affected while the other eye has completely normal findings, however, then the diagnosis of nutritional or toxic optic neuropathy is questionable. A gradual progressive blurriness, then cloudiness, often forms at the point of fixation.[1]

Signs

Visual acuity then declines rapidly or slowly to any level. Nutritional optic neuropathies usually result in visual acuity of 20/200 or better. A visual acuity of 20/400 or better is often seen in toxic optic neuropathies, except in methanol toxicity, which causes complete or nearly complete blindness. As visual acuity decreases, a protan defect develops. Because of the symmetric and bilateral visual impairment, a relative afferent pupillary defect is not often present. The pupillary light response may be bilaterally sluggish or absent. The pupils are often dilated in completely or nearly blind patients. The most common visual field defects seen in nutritional or toxic optic neuropathies are central and cecocentral scotomas. In nutritional optic neuropathies, the optic disc may be normal or mildly hyperemic in the early stages. Splinter hemorrhages may occasionally be seen on or off the hyperemic disc. Over a period of several months to years, papillomacular bundle atrophy and temporal disc pallor are followed by optic atrophy. In the early stages of toxic optic neuropathies, the optic discs usually appear normal. Disc edema and hyperemia are seen more often in acute intoxications. The severity and course of development of papillomacular bundle and temporal disc atrophy vary according to the type of toxin. For example, optic discs initially appear normal in ethambutol toxicity and then become atrophic if the drug is continued, whereas optic disc edema and flame-shaped hemorrhages are the initial presentation in amiodarone toxicity.[1]

Evaluation of a Nutritional/Toxic Optic Neuropathy

Evaluation of any patient suspected of having a nutritional or toxic optic neuropathy should include a detailed history of when a drug or toxin was ingested, family history, and dietary history. In toxic optic neuropathies, the visual loss may be acute or chronic. The onset of visual

symptoms occurring during or immediately after exposure to the specific toxin and the occurrence of similar illnesses in coworkers or others exposed to the same drug or chemical may help establish the etiology of the visual loss.[1]

In addition to the history and examination, magnetic resonance imaging (MRI) of the brain and orbits with contrast is required to rule out compressive and ischemic lesions, as bilateral central vision loss can occur from bilateral occipital lesions. MRI of the optic nerves and optic chiasm with and without gadolinium and diffusion tensor imaging may be needed to assess for signs of inflammation and/or demyelination.[1–3] Visual field testing by static or kinetic techniques is essential. Although central or cecocentral scotomas are more common in affected patients, bitemporal defects or peripheral field constriction may occasionally occur in patients with ethambutol or amiodarone toxicity, respectively. In any patient with bilateral central scotomas, laboratory investigation for B_{12} deficiency and folate deficiency must be performed.[1]

In diagnosing B_{12} (cobalamin) deficiency, serum B_{12} levels may be misleading because B_{12} may bind to transcobalamins, leading to falsely normal serum B_{12} levels, such as in hepatic disorders. Falsely low serum levels may be seen in folate deficiency or during pregnancy. When the serum B_{12} level does not definitely demonstrate deficiency, serum methylmalonate and homocysteine levels should be measured. These precursors of the cobalamin-dependent pathway are elevated in at least 85% of patients with B_{12} deficiency. Although these elevated levels of metabolites are not specific for B_{12} deficiency, they are useful in establishing the diagnosis of B_{12} deficiency when the serum B_{12} level is in the low to normal range (200–350 pg/mL).[4]

To determine the cause of the B_{12} deficiency, anti-parietal cell antibodies, which are present in about 85% of patients with autoimmune atrophic gastritis and anti-intrinsic factor antibodies which are more specific than sensitive for should be measured. A Schilling test to look for B12 malabsorption syndrome should also be performed by a gastroenterologist.[4]

A complete blood cell count and examination of the peripheral blood smear for any macrocytosis, macro-ovalocytes, and hypersegmented neutrophils is also required to establish the diagnosis of megaloblastic anemia, because B_{12} deficiency is associated with this disorder.[4]

Other laboratory tests in the workup of nutritional or toxic optic neuropathy include red blood cell folate levels, VDRL (Venereal Disease Research Laboratory), vitamin assays, serum protein concentrations, serum chemistry, urinalysis, and heavy metal screening, especially for lead, thallium, and mercury, and Leber's hereditary optic neuropathy genetic testing. Identification of the suspected toxin and its metabolite should be performed in the serum and urine (Tables 6.1 and 6.2).[4]

TABLE 6.1. Drugs, nutritional deficiencies, and toxins associated with toxic optic neuropathy (adapted from Miller and Newman[5])

Drugs
Antimicrobials: chloramphenicol, chloroquine, clioquinol, dapsone, ethambutol, iodochlorhydroxyquinoline, isoniazide, linezolid, streptomycin
Immunomodulators/immunosuppressives: cyclosporine, interferon-alpha, tacrolimus (FK506)
Chemotherapeutics: carboplatin, chlorambucil, cisplatin, 5-fluorouracil, methotrexate, nitrosureas (BCNU, CCNU, ACNU), paclitaxel, tamoxifen, 5-vincristine, cytosine arabinoside, purine analogues, procarbazine, cyclophosphamide, vinca alkaloids
Other drugs: amiodarone, amantidine amoproxen, cafergot, chlorpropamide, cimetidine, clomiphene citrate, deferoxamine, disulfiram, emetine, infliximab, pheniprazine, quinine, sildenafil
Nutritional deficiencies
Vitamin B_1 (thiamin), vitamin B_2 (riboflavin), vitamin B_{12} (cobalamin), folate
Toxins
Alcohol, arsacetin, carbon monoxide, carbon disulfide, carbon tetrachloride, cobalt chloride, ethchorvynol, ethylene glycol, hexachlorophene, iodoform, lead, mercury, methanol, methyl acetate, methyl bromide, octamoxin, organic solvents, perchloroethylene, pheniprazine, plasmocid, styrene, thallium, trichloroethylene, triethyl tin, tobacco, toluene, unshielded radiation exposure of more than 3000 rads

Table 6.2. Differential diagnosis of nutritional and toxic optic neuropathies (adapted from Miller and Newman[5])

- Arteritic ischemic optic neuropathy (giant cell arteritis)
- Nonarteritic ischemic optic neuropathy
- Infiltrative optic neuropathy (sarcoidosis)
- Infectious optic neuropathy (syphilis, Lyme, toxoplasmosis, herpes zoster)
- Optic neuritis from demyelinating disease
- Postradiation optic neuropathy
- Hereditary optic neuropathy (Leber's hereditary optic neuropathy, dominant optic neuropathy)
- Compressive optic neuropathy (orbital pseudotumor, thyroid eye disease)
- Autoimmune optic neuropathy (lupus)

Nutritional Optic Neuropathy

Vitamin deficiencies are now rare in the United States and in Western Europe. They are most likely to occur either associated with general malnutrition; as a complication of another disease, such as malabsorption or alcoholism; as a consequence of therapy, such as hemodialysis or total parenteral nutrition; or as a result of an inborn error of metabolism. The vitamin deficiencies, including vitamin B_{12}, vitamin B_1, vitamin B_2, and folic acid, cause central vision loss, dyschromatopsia, cecocentral scotomas, and a selective loss of the papillomacular bundle.[6]

Vitamin B_{12} Deficiency Optic Neuropathy

Vitamin B_{12} deficiency is the underlying cause of several syndromes of nutritional optic neuropathy. The optic neuropathy may be the initial manifestation in a patient when no other neurological signs of B_{12} deficiency, such as peripheral neuropathy and dementia, are evident. Eighty percent of affected patients are males.[7]

Vitamin B_{12} deficiency and its complications are more often seen in pernicious anemia, an autoimmune disorder resulting from antiparietal cell antibodies and antiintrinsic factor antibodies that inhibit the production of intrinsic factor that is required for absorption of vitamin B_{12} in the ileum. Pernicious anemia most often occurs in middle-aged and elderly Caucasians. Optic neuropathy may be the initial feature of pernicious anemia, preceding the development of megaloblastic anemia and even lower cervical and upper thoracic posterior column demyelination and leukoencephalopathy. Patients with pernicious anemia and no visual symptoms may have abnormal visual evoked potentials (VEPs) suggestive of subclinical optic nerve and/or optic chiasm lesions.[1]

Vitamin B_{12} deficiency leads to elevated levels of methylmalonyl CoA that interferes with fatty acid synthesis, resulting in abnormal myelin formation.[8,9] This subclinical optic neuropathy can be detected by delayed P100 latencies. B_{12} deficiency is also postulated to alter oxidative metabolism. It causes decreased levels of succinyl CoA, an integral component of the Kreb's cycle. It is thought that impaired oxidative metabolism leads to elevated levels of methyltetrahydrofolate (MTHF), required for converting homocysteine to methionine. As a kainate receptor agonist, MTHF causes excessive depolarization[10,11] and depletion of adenosine triphosphate (ATP).[12,13]

Because the parvoretinal ganglion cells[14] of the papillomacular bundle have a higher energy demand than the magnoganglion cells,[15] the papillomacular bundle would be most affected by ATP deficiency secondary to B_{12} deficiency. This vulnerability may explain the development of a cecocentral scotoma in B_{12} deficiency optic neuropathy. ATP deficiency may also explain the onset of optic neuropathy when no other neurological signs are evident. Furthermore, ATP deficiency may serve as a possible mechanism to explain Leber's hereditary optic neuropathy (LHON), tobacco-alcohol amblyopia, and other toxic optic neuropathies.[6]

The diagnostic evaluation of suspected vitamin B_{12} deficiency consists of checking serum cobalamin, serum methylmalonate, and serum homocysteine levels. Although not specific for cobalamin deficiency, the metabolites methylmalonate and homocysteine can help establish a diagnosis of cobalamin deficiency when serum cobalamin level is in the low-to-normal range (200–350 pg/mL) (Johnson et al.,[4] p. 364). Vitamin B_{12} levels below 100 pg/mL

often produce neurological manifestations. Antiparietal cell antibodies, which are more sensitive, and antiintrinsic factor antibodies, which are more specific, may both be used to identify patients with autoimmune atrophic gastritis. The cause of the vitamin B_{12} deficiency should then be evaluated by the Schilling test to determine the degree of cobalamin malabsorption. Because cobalamin deficiency is associated with megaloblastic anemia, complete blood cell count and examination of peripheral blood smear should be performed to look for macrocytosis with macro-ovalocytes and hypersegmented neutrophils.[4]

The treatment of vitamin B_{12} deficiency is cyanocobalamin 1000 µg IM three times weekly for the first 2 weeks, followed by maintenance therapy of 500 µg to 1000 µg IM monthly. This replacement therapy is lifelong in most circumstances. Some patients who discontinue maintenance therapy may experience recurrence of neurological symptoms. Reversal of symptoms and signs is greater with early and aggressive therapy. High-dose folate therapy corrects the megaloblastic anemia caused by cobalamin deficiency, but it does not improve and may even worsen the neurological disease.[4]

Combined Nutritional and Toxic Optic Neuropathies

Cuban Epidemic of Optic Neuropathy

Between 1991 and 1993, approximately 50,000 cases of nutritional optic neuropathy were reported during food shortages in Cuba. Most were adult men and women ranging from 25 to 60 years of age. Sadun et al.,[16] studied the Cuban epidemic of optic neuropathy and defined the following diagnostic criteria for this syndrome: Nerve fiber layer in the papillomacular bundle must be present with three of the five following symptoms or signs: (1) subacute bilateral visual loss, (2) dyschromatopsia, (3) cogwheel smooth pursuit, (4) central or cecocentral scotomas, or (5) impairment of contrast sensitivity.

In a study by Roman,[17] the 50,862 reported cases were analyzed further to reveal not only optic neuropathy, but also sensorineural deafness, peripheral painful sensory neuropathy, and dorsolateral myeloneuropathy. These clinical features were consistent with Strachan syndrome and beriberi, disorders resulting from a deficiency of micronutrients.[18,19] Most Cubans significantly improved after multi-B vitamin and folate supplements. Less than 0.1% of them had any sequelae.

Vitamin B_{12} and folate deficiencies and environmental factors, such as chronic methanol ingestion and cyanide exposure, probably contributed to this syndrome. It was thought that formate accumulation from folic acid deficiency and methanol ingestion could cause oxidative phosphorylation defects.[20] In a study of 34 affected Cubans with 65 controls by Gay et al.,[20] dietary factors were associated with the occurrence of epidemic neuropathy in Cuba. Smoking and alcohol consumption augmented the adverse effects of dietary deficiencies. The Cubans had a diet low in caloric energy, protein, fat, and micronutrients, with a disproportionate excess of sugar.

This acquired mitochondrial dysfunction from dietary-related ATP deficiency could also lead to this Cuban epidemic. Some reports have even shown the presence of LHON mutations, which could have further predisposed some Cubans to develop optic neuropathy. In a report by Johns et al.,[21] mitochondrial DNA mutations in two of nine Cubans with optic neuropathy and peripheral neuropathy had LHON mutation at nucleotide position 9438 and a novel mutation at nucleotide position 9738 in the cytochrome *c* oxidase subunit III gene. The stresses of poor diet, smoking, alcohol, and other environmental factors could have precipitated the clinical manifestation of LHON in these patients. LHON should be carefully distinguished from Cuban epidemic optic neuropathy.[22]

The affected Cubans in this epidemic who were treated with cyanocobalamine 3 mg/day and folate 250 mg/day within 3 months of onset of symptoms experienced visual recovery. In a study of 20 patients, average visual acuity recovered from 20/400 to 20/50, and average color vision on American Optical Color test plates improved from 2/8 to 7/8.[16]

Tobacco-Alcohol Amblyopia

The nutritional optic neuropathy in Cuba was also influenced by other environmental factors. Lincoff et al.[23] and Tucker and Hedges[24] described a clinical syndrome involving thiamine- and B_{12}-deficient optic neuropathy, glossitis, cheilitis, and cheilosis associated with cigarette smoking and alcohol consumption. This combined nutritional and toxic optic neuropathy is often called tobacco-alcohol amblyopia. It usually affects middle-aged men who are heavy smokers and alcoholics.[25] Subacute progressive, symmetric, painless bilateral visual loss, dyschromatopsia, and central or cecocentral scotomas are characteristic symptoms.[26–28] Tortuous small retinal vessels may be seen. The optic discs initially appear normal and then become pale later.[28]

The mechanism by which tobacco causes optic nerve toxicity is unclear, but it is believed that vitamin B_{12} deficiency and the cyanide in tobacco may play a role in optic nerve damage, possibly by demyelination.[29] Despite little change in current tobacco consumption in Western countries, new cases of tobacco-alcohol amblyopia have decreased, suggesting that nutritional deficiencies have an important role in this disorder. Other cases with no nutritional deficiencies detected have been associated with tobacco toxicity.[30] Cyanide and free radicals from the tobacco have been shown to decrease mitochondrial respiratory activity,[31] damage mtDNA,[32] and even cause changes in mitochondrial morphology.[33]

The treatment for tobacco-alcohol amblyopia is cessation of smoking and drinking. Visual recovery may be seen within a few weeks of treatment with hydroxycobalamine injections.[16]

Although only a few Cubans were affected by nutritional optic neuropathy, no specific genetic predisposition was identified in those who were affected. Some clinical features of tobacco-alcohol amblyopia were similar to those of LHON, but the prodromal symptoms of weight loss, polyuria, fatigue, and other neurological manifestations, such as myelopathy and peripheral neuropathy, appeared more consistently in Cubans with tobacco-alcohol amblyopia. Cogwheel smooth pursuit and visual recovery with vitamin supplementation also distinguished this epidemic disorder from LHON.[34]

Other Epidemics of Combined Nutritional/Toxic Optic Neuropathies

Other similar epidemics of nutritional optic neuropathy have also been studied in other parts of the world. Prisoners of war from Thailand[35] in 1945 and prisoners during the Korean war[36,37] developed nutritional amblyopia. With vitamin B complex supplementation, they recovered some vision as early as 2 weeks after therapy was initiated.

In Jamaica, Strachan's syndrome is associated with poor nutrition.[38] Bilateral visual loss with central or cecocentral scotomas and temporal disc pallor was associated with a painful sensory ataxic peripheral neuropathy and muscle atrophy. Gastric achlorhydria and malabsorption of B_{12} was found in most affected persons. Treatment with vitamin B after many years of visual loss did not promote recovery.

A Strachan-like syndrome was also discovered in Nigeria in the 1970s by Osuntokun and Osuntokun.[39] The 360 Nigerians with tropical amblyopia presented with gradual or rapid visual loss, color defects, and peripheral constriction in 84% of affected persons, rather than central scotomas. It was hypothesized that peripheral retinal damage may have contributed to the peripherally constricted visual fields, but 41% of affected persons had marked bilateral temporal disc pallor, similar to that seen in nutritional amblyopia. Cyanide from cassava beans, a staple food in Nigeria, was thought to have contributed to this disorder. Elevated levels of cyanocobalamin, plasma thiocyanate, cyanide, and urinary thiocyanate were all suggestive of cyanide exposure. A balanced diet helped improve vision, and a return to the cassava diet worsened vision.

Removal of the toxin may lead to some reversal of the optic neuropathy. Oral maintenance replacement therapy of thiamine 100 mg/day, folic acid 1 mg/day and vitamin B_{12} 1000 mg/day may be appropriate for those with additional folate deficiency. Folate treatment itself only reverses the megaloblastic anemia caused by cobalamin deficiency and does not improve

the optic neuropathy. Discontinuation of smoking and alcohol along with a well-balanced diet emphasizing green vegetables and fruit is critical for recovery in nutritional optic neuropathy.[4]

Folic Acid Deficiency Optic Neuropathy

Similar to B_{12}, folate is involved in methionine metabolism. Folate, in the form of methyltetrahydrofolate, donates a methyl group to homocysteine to form methionine and tetrahydrofolate. Tetrahydrofolate helps metabolize formate. Folate deficiency will lead to the accumulation of formate, which is also a toxic metabolite from methanol, causing optic neuropathy.[40] Folic acid deficiency causes other neurological manifestations, such as polyneuropathy and even subacute combined degeneration of the spinal cord. Although folate deficiency often occurs with other nutrient deficiencies, isolated folic acid deficiency was shown to cause optic neuropathy in a study by Golnik and Schaible[41] and in another study by Hsu et al.[42] The six patients with low folate levels but normal B_{12} levels developed bilateral visual loss, color defects, and central or cecocentral scotomas with optic discs that were normal or had temporal disc pallor. Measurement of erythrocyte folate, rather than serum folate, was found to be more sensitive in the early diagnosis of this disorder. With folate replacement therapy, their vision improved within 4 to 12 weeks of symptom onset.

Thiamine/B_1 Deficiency Optic Neuropathy

Several studies have shown that isolated thiamine deficiency can cause optic neuropathy. Children maintained on a ketogenic diet for seizure control[43] developed bilateral visual loss with cecocentral scotomas and low serum transketolase (an indication of thiamine deficiency) with normal B_{12} and folate levels. After replacement therapy, their vision recovered. Five patients with tobacco amblyopia who were treated with thiamine and an inadequate diet recovered vision within 6 weeks of onset of symptoms.[9] In another case report of a patient with ulcerative colitis who developed no light perception and oculomotor palsy, thiamine replacement therapy resulted in visual recovery within a few days.[44]

Vitamin E Deficiency Optic Neuropathy

Vitamin E deficiency causes progressive ataxia, arreflexia, ophthalmoplegia, and pigmentary retinopathy. Optic neuropathy has been reported in a patient with cholestatic liver disease[45] and vitamin E deficiency with normal B_{12} and folate levels; he developed optic disc pallor and pigmentary retinopathy. Visual evoked potentials were bilaterally extinguished, and the electroretinogram was abnormal.

Zinc Deficiency Optic Neuropathy

Zinc is required for the metabolism of vitamin A in the eye.[46,47] Zinc plays an important role in stabilizing microtubules for axonal transport. Zinc deficiency causes defective rapid axonal transport in vitro and therefore may contribute to the development of optic neuropathy.

Although zinc deficiency may cause abnormal rod function, it has been associated with optic neuropathy in acrodermatitis enteropathica, an autosomal recessive defect in intestinal zinc absorption. Six patients with acrodermatitis enteropathica have been documented with optic atrophy.[48]

Further evidence linking zinc deficiency with optic neuropathy has indirectly been shown in the chelation of zinc by ethambutol, which may cause optic neuritis. In a study of 84 patients with ethambutol toxicity, those with lower zinc levels (less than 0.7 mg/L) had a higher incidence of optic neuritis than those with serum levels greater than 1 mg/L.[49]

Iatrogenic Malabsorption Syndrome-Related Optic Neuropathy

A biliopancreatic bypass surgery to induce a malabsorption syndrome to treat morbid

obesity can be complicated by hypocalcemia with metabolic bone disease, a marked steatorrhea, and protein malnutrition[50] to cause a combined vitamin A deficiency and nutritional optic neuropathy. Visual function retuned to normal after oral vitamin and mineral supplementation.

Toxic Optic Neuropathy

Tobacco-Related Optic Neuropathy

See earlier section on tobacco-alcohol amblyopia.

Methanol-Associated Optic Neuropathy

Methanol, used as an industrial solvent and in automotive antifreeze, is one of the most common causes of toxic optic neuropathy. Formic acid, its metabolite, blocks mitochondrial pathways in the retina and optic nerve.[51] The symptoms of methanol intoxication are usually delayed for 12 to 18 h. During this latent period, methanol is oxidized to the more toxic formate, which then causes a metabolic acidosis, a hallmark of methanol intoxication. The degree of acidosis is an approximation of the severity of the intoxication. Drowsiness, headache, nausea, vomiting abdominal pain, and blurry vision are the common presenting symptoms and may be followed by blindness, coma, and cardiac arrest if intoxication is severe.[52] Permanent visual loss may occur within hours to days after ingestion of methanol.

Patients intoxicated with methanol may present with varying levels of visual loss, even with total permanent blindness. Central and cecocentral scotomas are usually present in patients with partial visual loss. In the early stages, the optic discs may be edematous and hyperemic with peripapillary retinal edema. Pupillary responses are often sluggish, and no response to light is indicative of a poor prognosis. Recovery of vision usually begins within a week, but in some cases, vision may worsen again after several weeks of improvement. The optic discs become pale with glaucomatous-like cupping, and the retinal arteries may appear attenuated.[1]

A serum methanol level greater than 20 mg/dL with a large anion gap, a high serum formate level, and a decreased serum bicarbonate level confirms the diagnosis of methanol intoxication. Administration of ethanol to interfere with the metabolism of methanol should be given, along with hemodialysis to remove the toxin and bicarbonate to restore acid–base balance. If treatment is delayed beyond the first several hours of ingestion of methanol, permanent visual damage may occur.[1]

Ethylene Glycol-Associated Optic Neuropathy

Ingestion of ethylene glycol, an active ingredient in automobile antifreeze, causes toxic symptoms similar to those of methanol, such as nausea, vomiting, abdominal pain, coma, and cardiac arrest. In contrast to the complications of methanol intoxication, renal failure occurs more often from ethylene glycol poisoning, and the frequency of visual loss is also much lower.[53] The optic discs may initially appear normal, followed by optic atrophy. In contrast to the visual findings in methanol toxicity, papilledema from increased intracranial pressure may be associated with nystagmus and ophthalmoplegia.[1]

The presence of oxalate crystals in the urine confirms the diagnosis of ethylene glycol intoxication. Glycolate, a metabolite of ethylene glycol, causes a metabolic acidosis and large anion gap. Therefore, treatment is similar to that for methanol intoxication, which includes bicarbonate, ethanol, and hemodialysis.[53]

Methanol-Induced Optic Neuropathy

Methanol intoxication may cause partial visual loss to irreversible blindness. In less severe cases, central and centrocecal scotomas predominate. Hyperemic disc swelling and some edema of the peripapillary retina may be seen. No pupillary reaction is indicative of a poor visual prognosis. Vision may improve within a week of discontinuation of methanol. Vision occasionally may worsen weeks after first improving. The optic

disc gradually becomes pale and may acquire cupping that mimics that in glaucoma. Retinal arteries may also be attenuated.

Methanol toxicity is mediated by formic acid, a metabolite. Methanol is catabolized to formaldehyde in the liver by alcohol dehydrogenase and catalase. Formaldehyde is then metabolized to formic acid by the liver and red blood cell aldehyde dehydrogenases.[54] Formate may block ATP production by inhibiting cytochrome oxidase,[55] which then can cause impaired axonal transport and loss of membrane polarity and conduction.[56] The disrupted salutatory conduction could lead to visual loss, and the axonal compression from retrobulbar disc swelling could obstruct anterograde axoplasmic flow.

Postmortem histopathological findings from four patients revealed that formate toxicity was selective for the retrolaminar optic nerve and the centrum semiovale.[57] Because cytochrome oxidase activity is lower in white matter than in gray matter,[58] oligodendroglia of the optic nerve and cerebral white matter could be more vulnerable to formate toxicity than neurons of the retina or cerebral cortex.[56]

The diagnosis of methanol intoxication is based on a serum methanol level of greater than 20 mg/dL, a large anion gap, a high serum formate level, and a reduced serum bicarbonate level.

Treatment of methanol toxicity includes administration of ethanol, which interferes with the metabolism of methanol, administration of bicarbonate to correct the metabolic acidosis, and hemodialysis to eliminate the toxin.[4]

Toluene Associated with Optic Neuropathy

Toluene inhalation can lead to a toxic optic neuropathy. In a study[59] of 15 patients with bilateral optic neuropathy secondary to toluene toxicity, treatment of all patients revealed that 6 patients had improved visual acuities of 2 or more lines, 3 of whom showed normal P100 peak latency in the pattern visual evoked cortical potentials (PVECP). The visual prognosis and the PVECP changes were identical in both eyes of all patients. Changes in visual field defects were not mentioned in the study. The PVECP abnormalities in these patients suggest that prolonged exposure to toluene can cause optic nerve damage.

Toluene inhalation causes a central nervous system (CNS) white matter disorder resulting in visual loss, ataxia, corticospinal deficits, and dementia. In contrast to demyelination, toxicity results in an increase in very long chain fatty acids. Axonal swelling and thinning of the myelin sheath of peripheral nerves have been demonstrated on histopathological studies.[60]

Amiodarone- and Digoxin-Associated Optic Neuropathy

Amiodarone, a diiodinated benzofuran derivative for the treatment of cardiac arrhythmias, has been hypothesized to be a cause of optic neuropathy. Unilateral and bilateral anterior ischemic optic neuropathies (AION) have been reported in patients using amiodarone. Because these patients have similar risk factors of cardiovascular disease and crowded optic discs, it is difficult to distinguish whether their AION is a manifestation of a vascular occlusive disorder or amiodarone.[61] However, the incidence of optic neuropathy appears to be higher in patients on amiodarone, ranging from 1.3% to 1.79%, compared with the age-matched incidence of AION of 0.3%.[62,63] Some patients who need to take amiodarone may have worse underlying cardiovascular risk factors than the general population and may already be at risk of developing AION.

Evidence for the association of amiodarone and optic nerve damage is still inconclusive. The toxic optic neuropathy does not develop simultaneously with the toxic peripheral neuropathy. The optic neuropathy is not dose related, reversible, and deymyelinating, as is the peripheral neuropathy. No dose-related or temporally related evidence for an increased frequency of toxic optic neuropathy exists, similar to that for the development of corneal deposits and peripheral neuropathy.[64]

Colored halos around lights are the most common ocular symptoms during amiodarone treatment. In amiodarone-related optic neuropathy, patients have mild or no visual complaints. In contrast to those of NAION, in which

the onset of visual loss occurs from days to weeks, visual symptoms are slowly progressive and may begin 1 to 72 months after the initiation of amiodarone. In contrast to NAION, in which the visual loss is rarely bilateral and simultaneous, amiodarone-induced optic neuropathy is characterized by bilateral, simultaneous, insidious loss of visual acuity up to 20/200, with bilateral disc edema persisting for months. Field defects are typically mild and peripheral (Table 6.3).[65,66]

In a review of 55 patients with amiodarone optic neuropathy, Johnson et al.[67] found that only 65% of patients presented with painless bilateral simultaneous optic disc edema and 35% of patients had acute unilateral disc edema. The spectrum of amiodarone-associated optic neuropathy was categorized as follows: (1) insidious, (2) acute onset, (3) delayed progressive, and (4) presence or absence of optic disc edema. The most common form of amiodarone-associated optic neuropathy presents insidiously in about 40% of patients. The second most common type presents with an acute unilateral or bilateral visual loss in about 30% of patients. About 15% of patients presented with a retrobulbar optic neuropathy in which the visual loss can be insidious or acute and in one or both eyes simultaneously. About 10% of patients taking amiodarone develop increased intracranial pressure greater than 200 mmH_2O. In 10% of patients, amiodarone-associated optic neuropathy has a delayed-progressive onset. These patients may report visual loss before any appearance of optic disc edema and may develop disc edema days to weeks after amiodarone is withdrawn because of the long half-life of amiodarone, up to 110 days.[67–69]

In this same study by Johnson et al.,[67] nearly 20% with amiodarone-associated optic neuropathy had 20/200 or worse on presentation. Although 40% experienced some improvement in visual acuity, most patients had no change in visual acuity after stopping the drug; 10% even had worsening of their visual acuity after drug withdrawal. Optic atrophy was the common end stage for all patients with corresponding persistent field defects, similar to those in NAION. The final outcome of visual acuity in patients with amiodarone-associated optic neuropathy 20/30 compared to 20/60 in patients with NAION. This comparison may not be accurate because the visual acuity from 50 patients with amiodarone optic neuropathy was compared with that from 420 patients with NAION in the Ischemic Optic Neuropathy Decompression Trial.[70]

The exact pathophysiology of amiodarone-induced optic neuropathy is unclear. Amiodarone, similar to other amphiphilic drugs, binds to polar lipids and accumulates within

Table 6.3. A comparison of neuro-ophthalmic features between NAION and amiodarone-related optic neuropathy (adapted from Johnson et al.[67])

Features	NAION	Amiodarone optic neuropathy
Medication use	Absent	Within 12 months of initiating amiodarone (median, 4 months)
Gender preference	Male same as female	Male more often than female
Incidence	2.3 to 10.2 per 100,000 and more than 50 years of age	About 2% in patients treated with amiodarone
Ocular laterality at presentation	Unilateral	65% bilateral and 35% unilateral
Visual acuity on presentation	20/20 to no light perception	20/20 to 20/200
Optic nerve cup-to-disc ratio	Small (less than 0.2) cup-to-disc ratio	Any cup-to-disc ratio
Increased intracranial pressure	Absent	Occasional
Duration of disc edema after NAION attack/after drug withdrawal	2 to 4 weeks	1 to 8 months (median, 3 months)

lysosomes.[71] According to Garrett et al.,[72] fenestrated peripapillary choroidal capillaries are permeable to amiodarone. The choroidal interstitial fluid containing amiodarone may allow drug-induced phospholipidosis, in which membrane-bound bodies with multilamellar inclusion bodies accumulate in astrocytes and ganglion axons. Histopathological studies have shown intracytoplasmic lamellar inclusions in large axons. The accumulation of these inclusions may impair axoplasmic flow to cause optic disc edema.[71]

Amiodarone toxicity to the optic nerve is dose related, varying from 200 mg/day to 1200 mg/day. Decreasing the dose of amiodarone may improve the optic disc edema, and discontinuation of the drug allows gradual recovery. Because the half-life of amiodarone is up to 100 days, amiodarone-related optic disc edema lasts months compared to the disc edema of NAION, which resolves within weeks. In contrast to the persistent field defects in NAION, the mild peripheral field defects may improve in amiodarone-related optic neuropathy. Concurrent use of digoxin with amiodarone may increase the known side effects of digoxin, such as dyschromatopsia, visual disturbances, and visual field defects. Because the association of amiodarone and optic neuropathy remain controversial in some cases, the decision to discontinue amiodarone in the treatment of life-threatening cardiac arrhythmias is best made by the cardiologist.[64–66]

Disulfiram-Associated Optic Neuropathy

Disulfiram, used in the treatment of chronic alcoholism, interferes with the metabolism of acetaldehyde, a metabolite of ethanol. Optic neuropathy may occur in patients who have abstained from alcohol and have continued to take disulfiram. The mechanism of toxicity on the optic nerve is unknown. Visual loss is usually subacute or chronic and symmetric with central or cecocentral scotomas. The optic discs are often normal initially and later become pale. The optic neuropathy usually recovers completely in 1 to 5 months after discontinuing disulfiram.[1]

Ethambutol-Associated Optic Neuropathy

Ethambutol, used in the treatment of *Mycobacterium tuberculosis*, is metabolized to a chelating agent that may impair the function of metal-containing mitochondrial enzymes, such as the copper-containing cytochrome c oxidase of complex IV and the iron-containing NADH: Q oxidoreductase of complex I. This damage to the mitochondrial respiratory chain may lead to the development of optic neuropathy. Zinc may also play an important role in ethambutol toxicity of retinal ganglion cells.[73] Based on one postmortem study, demyelination of the optic chiasm was noted.[74]

Ethambutol toxicity to the optic nerve is dose dependent. Visual loss occurs more often in patients receiving 25 mg/kg/day or more. Visual loss does not develop until after treatment for at least 1.5 months and most often around 5 months. Visual loss can occur as late as 12 months after initiation of therapy.[75] More severe visual impairment may be seen in patients with impaired renal function because ethambutol is excreted by the kidneys.

Blue-yellow color defects, more commonly than red-green color defects, may be the initial presentation. Decrease in visual acuity is insidious and bilaterally symmetric. Visual field typically show central scotomas or bitemporal defects and, less commonly, peripheral constriction. Optic discs are initially normal, but may develop mild temporal disc pallor, if ethambutol is continued. Early diagnosis and prompt cessation of the ethambutol leads to a more favorable prognosis, because visual loss is usually irreversible.[76]

Chloramphenicol-Associated Optic Neuropathy

Chloramphenicol had been used to treat cystic fibrosis in children until 1970 when it was recognized that it caused a toxic optic neuropathy.[77] Children developed sudden-onset bilateral central visual loss with cecocentral scotomas. Selective damage to the papillomacular bundle and tortuous retinal vessels were often seen. Histopathology revealed retinal ganglion cell

loss and demyelination of the optic nerve, affecting mainly the papillomacular bundle.[78] Discontinuation of the drug and vitamin B complex treatment usually led to a recovery of visual function.

Linezolid-Associated Optic Neuropathy

Linezolid disrupts RNA translation by binding to the 23S ribosomal RNA of the 50S ribosome subunit to interfere with ribosome assembly. It is used in the treatment of methicillin-resistant *Staphylococcus*, vancomycin-resistant *Enterococcus*, nosocomial pneumonia, and complicated skin infections.[79] Linezolid has been associated with toxic optic neuropathy in which patients present with decreased visual acuity, dyschromatopsia, and cecocentral scotomas. Early discontinuation of the antibiotic results in gradual, but not full, visual recovery. Most reports of linezolid toxic optic neuropathy described patients with initial visual acuity of 20/200 or worse improving to 20/30 or better after discontinuation of the drug. Color defects, visual field defects, and optic disc pallor also improve.[79–83]

Linezolid-related optic neuropathy may be associated with the duration of linezolid therapy. During randomized clinical trials of this drug, the monitoring of adverse effects of linezolid continued up to the 28th day of treatment.[84] Several reports suggest that patients developed linezolid-related optic neuropathy after approximately 8 to 10 months of the standard dosage of 600 mg per day.[79,85] It is recommended that, if patients will be receiving this antibiotic for more than 28 days, they should be monitored with baseline and monthly eye examinations thereafter. Visual acuity, visual field, color vision, and dilated funduscopy should be performed.

Interferon-Alpha-Associated Optic Neuropathy

Interferon-alpha (IFN-α), a glycoprotein secreted by the immune system in response to viral infections, serves as intracellular signaling to enhance expression of specific genes, enhance and induce lymphocytes to kill target cells, and inhibit virus replication in infected cells.[86] Because IFN-α has anticytokine, antiviral, immunomodulatory, and antiproliferative activities, it has been used to treat chronic hepatitis B and C, cancer, and essential thrombocytosis.[86] It has been postulated that IFN-α can produce autoantibodies and subsequently cause deposition of immune complexes in the small arteries of the optic nerve. IFN-α can stimulate other cytokines, which may lead to an inflammatory reaction of the blood vessels that might subsequently induce ischemia.[87–89]

Anterior ischemic optic neuropathy is an uncommon complication of IFN-α treatment.[88] Two patients undergoing treatment with IFN-α developed bilateral simultaneous optic neuropathy within 3 months of starting this medication.[90] Bilateral optic disc edema and nerve fiber layer hemorrhages were associated with inferior nerve fiber bundle defects. Despite treatment with aspirin 300 mg/day after cessation of IFN-α in one patient, visual acuities and field defects remained unchanged. In the other patient, who was treated with IV methylprednisolone 1 g/day for 3 days with prednisone taper after IFN-α was discontinued, visual acuities improved but field defects persisted. NAION may occur within 1 week to 3 months of starting after IFN-α treatment in patients who do not have underlying vasculopathic risk factors for NAION.[90–95] The two patients reported by Purvin[89] developed sudden bilateral, sequential visual loss with disc-related field defects and segmental optic disc edema, all features characteristic of anterior ischemic optic neuropathy. The degree of disc pallor may depend on the severity of ischemia. Underlying anemia may decrease perfusion to the optic nerve to cause pallid optic disc edema.[90] Only one patient improved after discontinuation of IFN-α treatment.[93]

Infliximab-Associated Optic Neuropathy

Infliximab is a chimeric antibody of the IgG class that inhibits tumor necrosis factor-alpha (TNF-α) and is given intravenously for the

treatment of rheumatoid arthritis and Crohn's disease.[96] The inhibition of TNF-α has been associated, in rare instances, with the exacerbation of underlying demyelinating diseases, such as multiple sclerosis (MS).[87] High TNF-α levels have been found in MS plaques and mononuclear cells of patients with MS.[90] It has also been shown that the infusion of TNF-α in animal models of MS leads to worsening of their demyelinating disease. Infliximab has been associated with the development of retrobulbar optic neuritis.[97,98] In a study by Foroozan et al.,[97] two women in their fifth decade developed retrobulbar optic neuritis after treatment with influximab for rheumatoid arthritis and/or Crohn's disease. Their vision improved to baseline after discontinuation of the drug. Although these patients did not have underlying MS, it was postulated that TNF-α inhibition may have increased their risk for a demyelinating event.

Treatment with infliximab may also be complicated by a toxic optic neuropathy. After receiving three doses of infliximab for rheumatoid arthritis, three patients in their fifth and sixth decades developed acute bilateral disc edema with central, cecocentral scotomas, or inferior defects. Despite high-dose steroids, their vision did not improve. It was thought that the three cumulative doses of infliximab contributed to the development of their bilateral toxic optic neuropathy.[99]

Clomiphene Citrate-Associated Optic Neuropathy

Hormonal agents such as clomiphene citrate are often used in the treatment of infertility and can increase the risk of hypercoagulable complications. Visual disturbances occur in approximately 5% to 10%[99] of patients treated with clomiphene citrate. Optic neuritis has been reported during treatment with clomiphene.[100] Patients may develop transient blurry vision or "spots" in their vision. Anterior ischemic optic neuropathy has been reported in a 31-year-old woman with primary infertility after receiving a 5-day course of clomiphene citrate 50 mg orally each morning.[101] She developed acute right visual loss upon awakening with 20/200, a right relative afferent defect, decreased red saturation, and an inferior altitudinal defect in the right eye. The right optic disc was edematous and hyperemic with venous dilation and splinter hemorrhages. Two months later, her right visual acuity was 20/50 (–2), and she had right optic disc pallor.[102]

Tamoxifen-Associated Optic Neuropathy

Tamoxifen modulates estrogen receptor-α activity and is often used as either an adjuvant or a monotherapy in cancer treatment. The overall incidence of ocular toxicity is about 12%. Bilateral optic neuropathy rarely occurs, and early detection may help prevent permanent damage.[103]In a prospective study of 65 women with breast cancer who had a normal baseline eye examination and were started on oral tamoxifen 20 mg/day,[103] 12% developed ocular toxicity in which 7 had a keratopathy, 3 had bilateral pigmentary retinopathy, and 1 had bilateral optic neuritis. The patient with optic nerve involvement had residual optic nerve pallor and decreased vision. The keratopathic changes were reversible with discontinuation of the drug. Yearly eye examinations were recommended for patients on long-term tamoxifen.

Sildenafil- and Tadalafil-Associated Optic Neuropathy

Sildenafil is indicated for the treatment of erectile dysfunction in men, but it has been shown to be associated with the development of NAION. It is a selective phosphodiesterase-5 (PDE5) inhibitor that facilitates the nitric oxide–cyclic guanosine monophosphate (cGMP) pathway to relax smooth muscle in the corpus cavernosum, allowing inflow of blood during sexual stimulation. It is also hypothesized that its partial inhibition of phosphodiesterase-6 on the outer retinal photoreceptors causes a transient bluish tinge or haze to the vision and increased light sensitivity.[104]

At least seven men so far have been reported in the literature to have NAION from sildenafil.[104,105] In the cases of sildenafil associated with NAION reported by Pomeranz et al.,[105,106] the

patients ranged in age from 42 to 49 years old, and three of the five men had no cardiovascular risk factors. Two were taking aspirin on a daily basis, but the dose was not specified. Four of the men experienced acute loss of visual acuity within approximately 45 min to 12 h of drug intake. The dose of sildenafil ranged from 50 mg to 100 mg. One man had taken 50 mg sildenafil each week, and his visual fields gradually worsened over the 15-month period. The visual disturbances occurred after the first dose in one patient and after two or three doses in another patient. Two of the men had been using sildenafil irregularly for about 2 years. The duration of treatment was not reported in the fifth patient. Visual changes often occurred unilaterally and were accompanied by headache in one patient and by intraocular pain in another. All these men had small cup-to-disc ratios. After about 2 to 9 months of follow-up in four of the men, all had permanent peripheral constriction, and three of the four men had persistent reduction in visual acuity. In another report by Akash et al.,[107] a 54-year-old man developed permanent blindness in his left eye from NAION combined with a cilioretinal artery obstruction after an overdose of Viagra.

Structural features of the optic disc in patients affected by sildenafil may increase the risk of developing NAION. Small physiological cups are more common in patients with NAION, and it is believed that the crowding of nerve fibers through a small scleral canal causes the fibers to be more susceptible to ischemic damage.[107–109] The close temporal relationship between the use of sildenafil and NAION in patients with small cup-to-disc ratio in the unaffected eye and no vascular risk factors also suggests a possible causal relationship.[104,110–113]

Nitric oxide generated by sildenafil may be a possible toxic agent to the optic nerve and retinal ganglion cells. It has been shown that inhibition of nitric oxide synthetase decreased retinal ganglion cell damage in animals with glaucomatous optic neuropathy.[114] Nitric oxide is also a potent vasodilator and may interfere with autoregulation of blood flow to the optic nerve head.[115] Alteration in the perfusion of branches of the posterior ciliary artery that supply the optic nerve head has been implicated in NAION. Based upon Hayreh's theory that nocturnal hypotension could lead to ischemia in patients with a small cup-to-disc ratio, sildenafil could accentuate physiological nocturnal hypotension enough to decrease the perfusion pressure in posterior ciliary arteries.[111] In a study of 15 young, healthy males with a mean age of 39 years who underwent ocular blood flow measurements after oral ingestion of sildenafil 100 mg, none developed permanent or transient visual loss, and no significant change in the optic nerve rim or foveolar choroidal blood flow was observed after treatment with sildenafil.[116] The exact pathophysiology of sildenafil in NAION remains uncertain.

Tadalafil, another related drug for erectile dysfunction specific for cGMP PDE5 inhibitor, has been associated with NAION.[117–120] Bollinger and Lee[118]reported a 67-year-old man with hypercholesterolemia who experienced an episode of transient, inferior blurring of the visual field within 2 h after each of four doses of tadalafil taken several days apart. Three days later, he took the fifth dose and developed a permanent right inferior visual field defect. He had right optic disc edema, and his normal left optic disc had a small cup-to-disc ratio. The visual field loss after repeated ingestion of tadalafil suggested that PDE5 inhibitors could be a risk factor for the development of NAION.

Vardenafil, another PDE 5 inhibitor for erectile dysfunction, may also have the potential to cause NAION, but there have been no reports yet.

Radiation-Induced Optic Neuropathy

Radiation-induced optic neuropathy is an ischemic process, usually presenting as a posterior ischemic optic neuropathy, about 18 months after radiotherapy and after cumulative doses of radiation greater than 50 Gy or single doses greater than 10 Gy. It is often seen as a complication of radiation therapy in the paranasal sinus and skull base regions; and postoperatively for pituitary adenomas, parasellar meningiomas, frontal and temporal gliomas, craniopharyngiomas, and intraocular tumors.[121–125] The range between safe and unsafe radiation doses may

vary depending on individual tolerance. Previous or concurrent treatment with chemotherapy, such as methotrexate, ara-C, vincristine, ara-C, and other multiple drug combinations, can increase the risk of developing radiation-induced optic neuropathy. Radiation may alter cellular structures, such as the blood–brain barrier permeability, or arachnoid granulations, to change the pharmacokinetics of drug distribution and clearance. For example, methotrexate administered concurrently or after radiation therapy is more toxic than when it is given before radiation treatment. Radiation is thought to increase blood–brain barrier permeability so that more methotrexate enters the CNS.[126,127] Therefore, the toxic effects of these chemotherapeutic drugs can potentiate the adverse effects of radiation and vice versa.[128,129]

Radiation dose per fraction, total dose, total duration of treatment, volume of tissue irradiated, and the type of radiation (proton, electron, or neutron) can also affect the risk of developing radiation-induced optic neuropathy.[130] When the total dose, fraction size, or volume increases, the frequency of complications increases, but the latency to the onset of complications is decreased.[130–132]

Preexisting medical disorders, such as diabetes and endocrinological disturbances from Cushing syndrome or growth hormone-producing tumors, are additional risk factors.

Radiation-induced optic neuropathy is a form of late delayed radiation neurotoxicity that affects the white matter months to years after exposure of the anterior visual pathways to ionizing radiaton.[133] It is thought that radiation damages the DNA of normal tissues to initiate free radical-mediated damage of the vascular endothelium and glial cells in the white matter.[134–146] The number of vascular endothelial cells is reduced in experimentally radiated rat brains depending on the dose and the time of exposure.[137] In a case-controlled study by Levin et al.,[139] histological features were studied in optic nerves of 16 enucleated eyes from patients with uveal melanoma treated with proton beam irradiation, 6 from normal eyes, and 5 from eyes with nonradiated uveal melanomas. An increase in radiation dosage to the optic nerve was associated with a decrease in the number of endothelial cells. Endothelial cell counts did not correlate with age, gender, visual acuity, or time interval after radiation treatment. In another study of 34 patients with late delayed radiation-induced injury using proton magnetic resonance spectroscopy,[140] *N*-acetyl aspartate (NAA)/creatine and NAA/choline ratios decreased in areas with worsening brain injury. Because choline was not elevated in areas of mild to moderate brain injury, demyelination or glial hyperplasia was not a likely primary mechanism of late delayed radiation-induced injury. Unlike other types of ischemia, the ischemia in radiation-induced optic neuropathy involves a gradual decrease in oxygen gradient from normal tissue to damaged tissue. This gradual oxygen gradient is not conducive to cellular repair. On histology, radiation-injured optic nerves show obliterative endarteritis, endothelial hyperplasia, and fibrinoid necrosis replacing axonal and myelin loss.[141,142]

Radiation-induced optic neuropathy presents with acute, progressive visual loss in one eye or both eyes over weeks to months. Bilateral sequential visual loss is more common and it is usually painless. Rarely is the interval between optic disc involvement as long as 7 months, according to Lessell.[143] Transient visual loss may be a premonitory symptom before radiation-induced optic neuropathy is diagnosed several weeks later.[143] Visual symptoms usually develop about 18 months after treatment is completed, but the latency is variable.[121,143,144] Visual loss is irreversible, but spontaneous improvement has occasionally been reported in patients who have radiation papillitis.[145]

The final visual acuity in most patients with radiation-induced optic neuropathy is 20/200 or worse.[146] The visual field may show altitudinal defects or central scotomas. If the distal optic nerve is affected, then a junctional syndrome with an optic neuropathy and a contralateral temporal hemianopsia may be seen.[147] A retrobulbar optic neuropathy is most common. The optic disc may initially appear normal and then become pale over 4 to 6 weeks.[121] After orbital or intraocular radiation, radiation papillopathy, affecting the anterior disc, may be seen. Optic disc edema is associated with subretinal fluid,

peripapillary exudates, and cotton wool spots. The optic disc then gradually becomes pale.[121]

The differential diagnosis of radiation-induced optic neuropathy includes recurrence of the primary malignancy, arachnoiditis, a new radiation-induced parasellar tumor, and secondary empty sella syndrome with optic nerve and chiasmal prolapse.[148–150]

MRI of the brain and orbits with gadolinium and T_1-weighted fat saturation of the orbits is the diagnostic procedure of choice to differentiate tumor recurrence from radiation-induced optic neuropathy.[151–154] On T_1-weighted enhanced images, the injured optic nerves may occasionally enhance, and this enhancement usually resolves in several months. Radiation injury to the anterior visual pathways cannot always be detected in the early stages. In a postmortem study[155] of a 38-year-old man who was treated with interstitial brachytherapy (iridium-192 at 47 Gy) followed by limited-field irradiation of 45 Gy, the extent of injury[142] measured by MRI scan underestimated the damage seen on histology. Furthermore, MRI findings of radiation injury can even be occasionally seen before the neuro-ophthalmologic manifestions.[142]

Treatment for radiation-induced optic neuropathy has been controversial. Corticosteroids and anticoagulants have offered limited success. Corticosteroids may not be the ideal treatment because radiation injury does not involve vasogenic edema or inflammation. Heparin and warfarin have been shown to be effective in increasing cerebral blood flow in five of eight patients with cerebral radionecrosis, who experienced neurological improvement, but these drugs have not been shown to be beneficial in improving vision of patients with radiation optic neuropathy.[156] In a report by Barbosa et al.,[157] anticoagulation treatment in a patient with bilateral radiation-induced optic neuropathy resulted in no visual improvement. Radiation optic neuropathy has also been reported to occur despite patients being on anticoagulation during radiation treatment and during the time of visual loss.[157–159]

Evidence now shows that hyperbaric oxygen therapy appears to be a more effective therapy for radiation-induced optic neuropathy. It alters the oxygen gradient so that capillary angiogenesis is possible.[160] In a review by Borruat et al.,[161] patients receiving hyperbaric oxygen therapy with greater than or equal to 2.4 atmospheres experienced the best visual outcome compared to those who received no treatment and to those who received 2.0 atmospheres. Further review of data from previous cases suggested that hyperbaric oxygen therapy should be started as early as possible after the onset of visual loss. Treatment should consist of 30 sessions of 90 min each so that patients are breathing 100% oxygen at a minimum pressure of 2.4 atmospheres.

Based upon the experience and data of various treatments, some management strategies have evolved to help improve visual outcome. If one eye has been affected, serial eye exams must be done over the 10- to 20-month period after treatment to monitor for any signs of recurrence in the fellow eye because bilateral sequential involvement is not uncommon. Serial MRIs of the brain and orbits should be performed over the 20-month period after radiation therapy is completed. Subclinical evidence of radiation necrosis on MRI should be treated with prophylactic hyperbaric oxygen therapy.[142] VEP may also play a role in detecting early radiation-induced optic neuropathy when the eye exam is normal. In a prospective study of 28 patients who underwent radiation therapy for uveal melanomas,[162] 18% of patients had no clinical signs of optic neuropathy, but 50% developed abnormal VEPs, suggesting that subclinical radiation optic neuropathy had developed in some patients. Radiation-induced optic nerve injury may be more frequent than clinically expected.

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7
Hereditary Optic Neuropathies

Jane W. Chan

Leber's Hereditary Optic Neuropathy

Leber's hereditary optic neuropathy (LHON) is a painless, bilateral, acute or subacute optic neuropathy that is maternally inherited from mutations in the mitochondrial DNA. The exact worldwide incidence of LHON is unknown, but it is much less prevalent than other optic nerve disorders, such as optic neuritis and ischemic optic neuropathy. Men are affected two to three times more frequently than women.[1–3]

Symptoms and Signs

Visual loss usually occurs during the second to third decades,[3,4] with a mean age of 27 years and a reported range of 1 to 70 years. Painless unilateral loss of visual acuity develops with color desaturation over weeks and often is severe, decreasing to 20/200, counting fingers, or even no light perception by 6 weeks. The eyes can be affected simultaneously or sequentially, with an average interval between eyes being affected of about 2 months and a range of 6 to 22 weeks, and rarely 8 years or longer.[3,4] Monocular or subclinical involvement is even more rare.[5] Both eyes are affected sequentially in 78% of cases and simultaneously in 22%.[6] Sudden, complete blindness can occur in about 3.7 months, and then may worsen over a period of about 2 years. The final visual acuity can range from 20/50 to no light perception, depending on the type of mutation. The most severely impaired bp (base pairs) 11778 patients may have no light perception; the most severe bp 3460 patients may retain light perception; the severe bp 15257 patients will perceive hand motions; and the severe bp 14484 patients will be able to count fingers.

As visual loss progresses, a red-green color defect develops. Pupillary light reflexes are relatively spared. The central or cecocentral scotoma may be relative and then later may become large and absolute. During the acute stages, the optic disc is hyperemic. Capillaries, medium-sized arteries, and venules become more tortuous with arteriovenous shunting in the peripapillary vasculature.[7] The classic triad of acute LHON signs includes (1) circumpapillary telangiectatic microangiopathy in 30% to 60% of eyes, (2) swelling of the nerve fiber layer around the disc (pseudoedema), and (3) absence of fluorescein leakage from the disc or papillary region, which distinguishes LHON from a swollen optic disc (Figure 7.1).[7–10] Only 58% of patients with the bp 11778 mutation show telangiectatic vessels in the acute phase[1] and 33% with the bp 14484 mutation.[3] The telangiectatic vessels and pseudoedema of the disc resolve over several months. Optic atrophy develops with the most severe atrophy in the papillomacular nerve fiber layer. Microangiopathy is uncommon after 6 months.[3] Optic atrophy has been reported to be seen as early as 1 month from the onset of visual symptoms, but it is universally seen after 6 months.[3] Nonglaucomatous cupping of the optic disc and arteriolar attenuation may also develop.

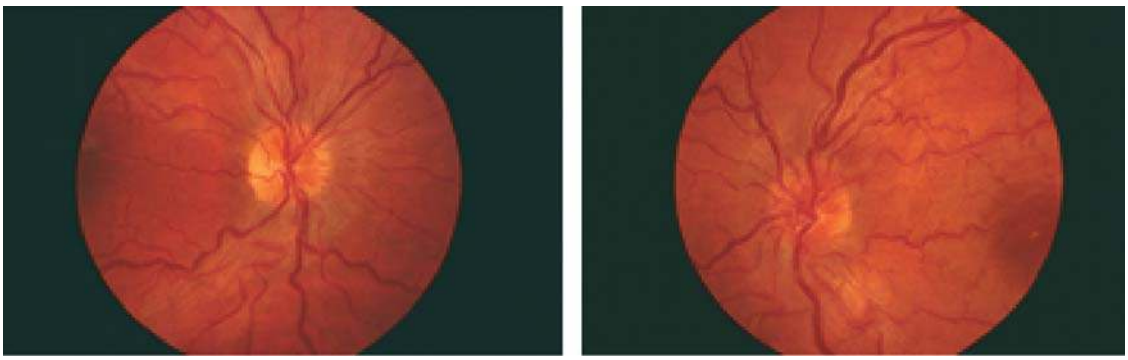

FIGURE 7.1. Leber's hereditary optic neuropathy. Since acute right visual loss occurred 6 weeks previously, the right optic disc (*right*) is slightly edematous and vascular tortuosity is less marked than in the left eye (*left*). It is gradually becoming more pale. Because of recent acute left visual loss, the left optic disc is more edematous with peripapillary telangiectasia. (Reprinted from Spalton et al.,[10] with permission from Elsevier.)

The characteristic funduscopic findings are not always present in affected persons with LHON who present with visual loss. Abnormal funduscopic findings may also be seen in presymptomatic patients and in asymptomatic maternal relatives who carry mitochondrial mutations associated with the disease. Swelling in the peripapillary retinal nerve fiber layer, increased tortuosity of capillaries, medium arteries and venules, and arteriovenous shunting have been reported in presymptomatic individuals and asymptomatic carriers.[7,8] Presymptomatic at-risk patients may show color defects on Farnsworth–Munsell 100-hue test and even mild abnormalities in the pattern-reversal visual evoked responses.[11]

Other ocular manifestations have been observed in LHON patients. LHON may also be a neuroretinopathy with a broad spectrum of genotype-specific phenotypes. Mann et al.[12] reported peripheral retinal phlebitis has been observed in a patient with LHON who harbored the 11778 mutation. In addition to bilateral central visual loss associated with headache, the patient had vitritis, vasculitis, and optic neuritis. Multiple sclerosis and other causes of vasculitis were ruled out.

Diagnostic Testing

The diagnosis of LHON can be confirmed by genetic testing on whole blood for the main primary mutations: 11778, 3460, 15257, and 14484. If these tests are unremarkable, then the secondary mutations of LHON can be tested.[3]

Although magnetic resonance imaging (MRI) of the brain and orbits is typically normal in patients with LHON, two LHON patients were reported to have abnormal enhancement of the optic nerves and chiasmal enlargement on MRI.[13] MRI of the orbits in some patients can also show increased T_2 signal in the affected optic nerve.[14] The optic nerve is affected in the mid- and posterior intraorbital sections, with sparing of the anterior portion. Cerebral mitochondrial dysfunction and damage in LHON patients has also been shown on phosphorous-31 magnetic resonance spectroscopy and magnetization transfer imaging.[14]

Optical coherence tomography (OCT) studies[15] have shown that the retinal nerve fiber layer (RNFL) in patients with LHON is thickened in the early stages of the disease of less than 6 months duration. Beyond 6 months, the RNFL is thinned, and some may be partially preserved in patients with atrophic LHON who have some visual recovery. The temporal fibers, which correspond to the papillomacular bundle, are usually the first and most severely affected, whereas the nasal fibers appear to be partially spared in the later stages of the disease. Patients with subclinical LHON have preferential involvement of the papillomacular bundle. On OCT, unaffected carriers with the 11778 muta-

tion have thickening of the temporal RNFL fibers.[15] Based on the OCT findings of Barboni et al.[15] and Savini et al.,[16] patients with LHON may not have monophasic symptoms and signs, but may manifest a latent phase with axonal thickening associated with normal visual function preceding clinically significant vision loss, followed by an acute phase of axonal injury with clinically significant visual loss. A chronic phase of spontaneous visual improvement may follow in some patients who have a lower probability of recurrence of visual loss.

Visual Prognosis of LHON

The visual prognosis is variable in patients with LHON. Optic atrophy with permanent severe central visual loss with relative preservation of pupillary light responses is the usual endpoint of the disease. However, recovery of central vision may occur years after severe visual loss. Spontaneous improvement of visual acuity has occasionally been reported even years after onset.[17–19] The visual recovery may occur progressively over 6 months to 1 year after initial visual loss, or even suddenly 2 to 10 years after onset. Contraction of the scotoma or reappearance of small islands of vision within the large central or cecocentral scotoma may develop. This recovery is commonly bilateral and symmetric. Once recovery occurs, visual loss does not usually recur. However, recurrent episodes of visual loss throughout life, leading to further worsening of vision, have been described.[20] The best visual outcome appears to be associated with the T14484C mutation in which 71% of patients have 6/24 or better.[2,17] Early age of onset of visual loss, usually less than 20 years of age, and the presence of the T14484C mutation are the most favorable prognostic factors.[2,3] In contrast, the G11778A and G3460A mutations seem to be associated with a poor visual outcome, ranging from 1/60 to 3/60. The G11778A mutation may have a later onset[6] and is most severe in one-third of affected females.[3]

The probability of visual recovery also varies in relation to the mutation, with only 4% of bp 11778 patients showing recovery an average of 36 months after onset, 22% of bp 3460 patients recovering after 68 months, 28% of bp 15257 patients recovering after 16 months, and 37% of bp 14484 patients recovering after 16 months.[1] Only 5% of patients have vision better than 6/60.[3]

Systemic Associations with LHON

The onset of visual loss may occasionally be associated with headache or ocular discomfort in 24% of patients.[3] Other systemic symptoms resembling those in multiple sclerosis have also been reported, such as Uhthoff's phenomenon, manifesting as transient worsening of vision with exercise or heat.[21]

Up to 9% of patients with LHON have associated cardiac preexcitation syndromes. Among Finnish patients, preexcitation syndromes including Wolff–Parkinson–White and Lown–Ganong–Levine are common.[4] Prolongation of the corrected QT interval was also observed in an African American family with the bp 11778 mutation.[22]

Patients with LHON, particularly those with the bp 11778 mutation,[1,23,24] may have symptoms and signs consistent with multiple sclerosis (MS) at the time of onset of progressive visual loss.[25,26] Most of these patients are female who have cerebrospinal fluid (CSF) and MRI abnormalities consistent with MS. Five percent of LHON patients with the bp 11778 mutation have a relative with MS.[25] Primary LHON mutations occur in some MS patients with severely affected optic nerves, but not in patients with MS as a whole.[26] Both disorders, LHON and MS, are thought to occur coincidentally because the prevalence of both diseases is no greater than that of each one alone. An underlying LHON mutation may also worsen the prognosis of optic neuritis in patients with MS.

Some pedigrees of LHON have a "Leber's plus" syndrome with more severe neurological abnormalities: (1) optic neuropathy, movement disorders, spastic paraparesis, psychiatric abnormalities, skeletal changes, and acute infantile encephalopathic episodes; (2) optic neuropathy, dystonia, and basal ganglia lesions on neuroimaging; (3) optic neuropathy and myelopathy; and (4) optic neuropathy and fatal encephalopathy in early childhood.[22,27–29]

An even wider range of clinical presentations was observed in two LHON families with more deleterious mtDNA genotypes. In the Australian pedigree harboring the MTND1*LHON4160C + MTND6*LHON14484C mtDNA haplotype, the family was homoplasmic for both mutations, but family member presentation ranged from being asymptomatic, to just having optic atrophy, to developing severe neurodegenerative disease. The most severe symptoms were observed in 9 of 56 maternal relatives and included headache, vomiting, focal or generalized seizures with a hemiparesis that generally resolved, and cerebral edema.[30] Specific neurological symptoms in this family included dysarthria, deafness, ataxia, tremor, posterior column dysfunction, corticospinal trait dysfunction, and skeletal deformities.[30]

The American Hispanic family[27] harbored a Native American mtDNA and was heteroplasmic for the MTND6*LDYT14459A mutation.[31] Maternal relatives in the pedigree ranged from being normal, to having adult-onset optic atrophy, to developing dystonia associated with bilateral striatal necrosis. One interesting feature of this pedigree was that LHON predominated in the earlier generations whereas dystonia predominated in the more recent generations. The phenotype associated with dystonia and striatal necrosis could have been considered part of a spectrum of LHON.

The broad spectrum of clinical manifestations that can occur in LHON is further shown in this family with a homoplasmic 14459G-A mtDNA mutation of the ND6 gene.[31] A 3-year-old girl with anarthria, dystonia, spasticity, and mild encephalopathy had bilateral, symmetric basal ganglia lucencies associated with cerebral and systemic lactic acidosis. Her maternal first cousin presented with a limp and mild hemiparesis along with similar MRI findings with a much milder phenotype. Other family members with the mutation were either asymptomatic or symptomatic with variable clinical and laboratory features, confirming the heterogeneous phenotype of homoplasmic 14459G-A mtDNA mutations, even within the same family.

Funalot et al.[32] reported three unrelated patients with LHON harboring mtDNA mutations at position 3460 of the MTND1 gene and positions 14459 and 14484 of the MTND6 gene. In addition to visual loss, each patient developed a complicated neurological syndrome resembling Leigh syndrome. Features included gaze palsy, hearing loss, spastic ataxia, cerebellar ataxia, rigidity, hyperreflexia, and multiple hyperintensities in the brainstem.[33]

Histopathology of LHON

On histopathology, ganglion cell loss occurs mostly in the central retina. Small axons in the papillomacular bundle, located centrally in the optic nerve, appear to be most affected.[34,35] Histopathological investigations also demonstrate a selective loss of the P-cell population and their corresponding smaller retinal ganglion cells, and a relative preservation of the M cells in the optic nerve.[35] These findings correlate with the fundus changes of early papillomacular bundle loss, dyschromatopsia, central scotoma, and preservation of pupillary light response in LHON patients.

Some ultrastructural studies of the muscle from affected patients have demonstrated enlarged, subsarcolemmal mitochondria, proliferation of cristae, and paracrystalline inclusions.[35,36] In a patient from the Queensland 1 pedigree with mtDNA 4160 and 14484 mutations, electron-dense calcium mitochondrial inclusions within ganglion cells were observed.[37]

Pathophysiology of LHON

LHON is transmitted by mitochondrial, non-Mendelian inheritance. Because mitochondria are maternally inherited,[38] no male-to-male transmission can occur in a LHON pedigree. The mitochondrial genome encodes 37 of the genes in the oxidative phosphorylation system and 13 of the protein subunits. Because most of the cellular adenosine triphosphate (ATP) is generated in this system, mutations in mtDNA contribute to defects in the oxidative phosphorylation system. The optic nerve, as well as the retina and extraocular muscles, are the ocular organs most affected as they are heavily ATP dependent. Complex I dysfunction leads to a

reduction of ATP synthesis and an increase of reactive oxygen species, predisposing neuronal cells to apoptosis.[39–41]

The unmyelinated, prelaminar portion of the optic nerve, including the retinal nerve fiber layer and the portion of the nerve crossing the lamina cribrosa at the optic nerve head, has a high number of mitochondria, as shown on electron microscopy (EM).[42] As the axons acquire myelin posterior to the lamina cribrosa, the number of mitochondria decreases, as shown on EM and cytochrome C oxidase staining.[42] The thinly myelinated, energy-demanding papillomacular bundle, especially at the prelaminar, unmyelinated portion of the optic nerve head, would be most vulnerable to complex I dysfunction because transmitting action potentials along unmyelinated fibers demands a high amount of energy. Histopathological features of optic nerve degeneration seen in LHON patients have demonstrated evidence of impairment of axonal transport.[35] Axoplasmic stasis and swelling with intramitochondrial calcification may ultimately lead to apoptosis, as shown in LHON cybrid studies.[37,39–41] Abnormal oxidative phosphorylation and decreased ATP production, along with free radical production, are thought to cause permanent damage to retinal ganglion cells and their axons.[43] Glial cells, which can upregulate nitric oxide synthase when activated, may play an important role in the cascade of events that lead to retinal ganglion cell death.[43]

Molecular Genetics and Genetic Heterogeneity of LHON

Three mtDNA mutations account for 95% of LHON cases. Thirteen percent of cases are from the G3460A mutation, 69% of cases are from the G11778A mutation, and 14% of cases are from the T14484C mutation.[45] The G11778A mutation produces substitution in the ND4 subunit of complex I. Mutations at n 3460 and 14484 produce A52T and M64V substitutions in the ND1 and ND6 subunits of complex I, respectively.[45]

Mutations of LHON are classified as primary or secondary mutations. The primary ones are found in multiple LHON families and alter more highly conserved amino acids. The G11778A, T14484C,[46,47] and G3460A[46] mutations are the most common primary ones. Other more rare primary mutations include T14596A, C14498T, G13730A, G14459A, C14482G, and A14495G.[46,48]

The 14459 mutation gives rise to the most severe phenotype.[28] Variable clinical manifestations can range from being normal, to having late-onset optic atrophy, to having early-onset dystonia accompanied by bilateral basal ganglia degeneration. When the mutation approaches homoplasmy, the penetrance is high, with 48% of maternal relatives with pediatric dystonia, 10% with only visual loss, and 3% with visual loss and dystonia.[28,49]

The second most severe mutation and the most common cause of LHON is 11778. It accounts for more than 50% of European cases and 95% of Asian cases, but it has not been found in controls.[1,50] Although most patients with this mutation present with only visual loss,[1] one patient experienced visual loss at 37 years of age associated with cerebellar-extrapyramidal tremor. He then developed left-side rigidity related to bilateral basal ganglia lesions at 38 years of age.[51] The mutation has arisen repeatedly on different mtDNA lineages[52] and is occasionally found with other LHON mutations.[53] It is frequently heteroplasmic.[54] It is about 82% penetrant in males. The spontaneous visual recovery rate is only 4%.[1,55,56]

The 3460 mutation accounts for about 35% of European LHON and has not been identified in controls.[57] It has been observed on several mtDNA lineages and occasionally occurs with other LHON mutations. It is usually homoplasmic and is expressed in 69% of males. The spontaneous visual recovery rate is 22%.[56,57]

The fourth primary mutation is 14484. This mutation accounts for about 20% of European LHON patients and has not been observed in 250 controls.[56] It is commonly associated with specific mtDNA lineages, often in association with 13708, 15257, or 3394. It has been homoplasmic in every case but one.[56] It has a penetrance in males of 82%. The spontaneous visual recovery rate is 37%.[56]

The mildest primary mutation is 15257. It occurs in about 15% of LHON patients and in 0.3% of the general population.[58] The mutation has been observed on the same mtDNA lineage, usually together with the 13708 and 14484 mutations in all but one case.[59] This mutation is consistently homoplasmic and has a penetrance in males of 72%. The probability of spontaneous visual recovery is 28%.[56]

Secondary mutations are found at a lower prevalence in control populations and may represent polymorphisms. These secondary mutations often occur in association with a primary mutation or other secondary mutations. A less highly conserved amino acid is mutated. Secondary pathogenic mutations in LHON include G13708A, A4917G, T4216C, G9804A, G9438A, and G15257A.[53]

Heteroplasmy and Environmental Factors

Phenotypic expression of LHON may be the result of decreased mitochondrial energy production with expressivity being modulated by heteroplasmy, the proportion of mutant to normal mtDNA,[60,61] and by environmental factors.[56,62] Nuclear genes and mtDNA mutations in LHON may interact in complicated ways. Not all individuals with 100% of mutant mtDNA develop visual symptoms, which indicates that additional, yet unknown, precipitating factors may have a role in determining phenotype.[63] The quantity of mutant mtDNA is also not proportional to the severity of the phenotype and the degree of penetrance. Several studies showed that the ophthalmologic characteristics and penetrance in LHON families with both mutations, 11778 and 14484, were not markedly more severe than those of classic LHON families who carried just a single mtDNA mutation.[63]

In multifactorial genetic models, environmental factors, such as carbon monoxide, cyanide, and nitric oxide in cigarette smoke, have been thought to be precipitating factors for the development of optic atrophy. These toxins may reduce the oxidative phosphorylation capacity in patients who already have the genetic predisposition for developing Leber's optic atrophy. Cullom et al.[62] found that 2 of 12 patients previously diagnosed as having tobacco-alcohol amblyopia, based on a classic clinical presentation, tested positive for known LHON mutations, 1 patient for the 11778 mutation and 1 for the 3460 mutation. The fact that only a few patients who abuse tobacco and alcohol develop optic neuropathy has suggested an element of individual susceptibility.[64] Cullom et al.[62] proposed that susceptibility may be the result of an LHON-associated mitochondrial mutation. Furthermore, Sadun et al.[65] reported the ophthalmologic findings in 192 eyes from 96 maternally related individuals from a seven-generation Brazilian pedigree with LHON and the 11778/haplogroup J mutation. The findings demonstrated a significant influence of environmental risk factors, particularly smoking, for developing LHON and for the severity of its clinical expression. However, smoking did not correlate with the subclinical abnormalities detected in carriers. More recently, a large case-controlled study by Kerrison et al.[37] showed no significant association between tobacco or alcohol use and visual loss among individuals with LHON primary mutations.

Incomplete penetrance and predilection for males to develop visual loss implies that additional factors may play a role in modulating the phenotypic expression of LHON. Only about 50% of males and about 10% of females who have one of the three primary mutations actually develop optic neuropathy.[55,63,66] The clinical severity of this genetic disorder depends upon its penetrance. Of the men at risk for LHON, 20% to 60% have visual loss and 4% to 32% of women who are at risk are affected. Affected women are more likely to have affected daughters.

Gene Therapy, Neuroprotection, and Other Treatments

There is currently no treatment available that improves the final visual outcome in LHON. The long-term management of visually impaired patients is mainly supportive. In genetic counseling, it is important for LHON carriers to be made aware that it is currently not possible to predict precisely whether or when they will

become affected. In general, the two main predictive factors for visual loss are age and gender. Estimates of recurrence risks differ between sexes and vary among published reports. Males have a 50% to 60% lifetime risk of blindness compared to only 8% to 32% for females.

However, the prevalence of singleton families confirmed by molecular testing indicates that these values are overestimated. Using genetic analysis as the starting point, one Australian study proposed that the risk of visual loss for males with the 11778 mutation is 20% and for females is 4%.[67] Based on published age-dependent penetrance data, most patients experience visual loss in their late teens or early twenties, and the probability of becoming affected is minimal once past the age of 50.[68]

Various strategies of therapy for LHON, such as gene therapy and pharmacologic agents, are presently being investigated. Guy et al.[69] found that cybrid cells containing the G11778A mutation, found in 50% of LHON cases, showed a 60% reduction in the rate of complex I-dependent ATP synthesis compared to wild-type cells. Using "allotopic expression," a technique in which a mitochondrial gene is expressed in the nucleus and the protein product is then imported back to the mitochondria,[69] they transfected a fusion ND4 subunit gene into cybrids containing the G11778A mutation. Cybrid cell survival after 3 days was threefold greater for the allotopically transfected cells, and these cells showed a threefold increase in the rate of complex I-dependent ATP synthesis, to a level indistinguishable from that in normal cybrids. Guy et al.[69] suggested that this rescue of a severe oxidative phosphorylation deficiency was a promising therapy for LHON. Because of the high risk of bilateral visual loss in patients with LHON, the fellow eye could be treated after visual loss had occurred in the first eye. These results obtained in vitro still need to be confirmed in animal models before human studies can be considered.

The use of pharmaceuticals, such as coenzyme Q or its short-chain derivative idebenone,[70] can restore electron flow and prevent oxidative stress. The efficacy of idebenone for the treatment of LHON is controversial. It may be more effective as a preventive therapy before visual loss develops. Another antiapoptotic agent is brimonidine, the alpha-2 receptor agonist.[71,72] It exerts neuroprotective properties by maintaining mitochondrial membrane potential and Bcl2 upregulation. Brimonidine may be used after visual loss in LHON in an attempt to salvage the vision of the unaffected fellow eye. Inhibitors of inducible nitric oxide synthase (NOS-2)[73] also have been shown to provide neuroprotection of retinal ganglion cells in rat models of chronic glaucoma. These inhibitors of NOS-2 may also benefit LHON patients. As in glaucoma, excess NO produced by astrocytes expressing NOS-2 can cause retinal ganglion cell damage in LHON optic nerve heads.[74]

Neuronal regeneration after optic nerve damage may be promising, but it is limited by inhibitory factors. Growth-promoting substrates are being identified, and techniques of reactivation of embryonic axonal growth to induce regeneration in adult neurons are being investigated in the retinal ganglion cell system.[75]

Dominant Optic Atrophy or Kjer's (OPA1)

Incidence

Autosomal dominant optic atrophy (DOA), or Kjer's, or juvenile optic atrophy, is the most common hereditary optic neuropathy. This disorder is linked to the OPA1 locus on chromosome 3q28-qter.[76] The prevalence in Denmark ranges from 1 in 10,000 to 1 in 50,000. DOA has an insidious onset as early as 1 year of age, and most commonly an onset between 4 and 6 years of age, with almost no visual symptoms, except for nystagmus and poor vision in severely affected children.[76]

Symptoms and Signs

Visual loss is usually symmetric. Initial visual acuity is usually equally reduced in both eyes from 20/20 to 20/800, with only about 15% of patients eventually developing vision of 20/200 or worse later in life. Up to half of patients with dominant optic atrophy have mild, insidious

progressive visual loss in which the visual acuity decreases by about 1 line every 10 years of age. The rate of visual loss is not correlated with the initial visual acuity. The rate of visual loss is also not similar for members of the same pedigree. Sudden, unexpected decrease in visual function may occur.[77]

Patients with dominant optic atrophy often develop a tritanopic defect or, less often, a generalized dyschromatopsia. Some families of affected individuals have red-green defects. The severity of the color defect does not correlate with the degree of loss in visual acuity.[77–80]

Central, paracentral, or cecocentral scotomas are usually seen with normal peripheral fields, except for a characteristic chromatic inversion of the peripheral field. The field of tritanopes is more contracted to blue isopters than to red.[81] A larger visual field defect appears in individuals who have more severe disease. Most defects occur in the superotemporal region, and this location has not been explained.[82]

Optic disc excavation is frequently seen in end-stage DOA, and in normal-tension glaucoma (NTG),[83] and is reported in LHON.[22,83–86] In a study by Votruba et al.,[87] DOA patients with OPA1 mutations showed optic disc excavation with enlarged cup-to-disc ratio, frequent peripapillary atrophy, and temporal gray crescent, most of which are features also seen in glaucomatous optic neuropathy. The temporal aspect of the disc characteristically has a triangular wedge-like excavation and is pale without fine superficial capillaries (Figure 7.2).[9,10] The smallest fibers of the papillomacular bundle are affected in the temporal disc. In a study by Votruba et al.,[88] optic atrophy may be subtle involving the temporal aspect of the disc in 55% of patients, or may involve the entire disc in 44% of patients. Fournier et al.[89] examined optic disc morphology in patients with DOA to elucidate features that would distinguish DOA from NTG. The DOA patients had a mild to moderate reduction in visual acuity and color vision. Seventy-eight percent had a temporal wedge-shaped area of optic disc excavation. All involved eyes had moderate to severe pallor of the temporal neuroretinal rim, with milder pallor of the remaining noncupped rim. All eyes had a slate-gray crescent within the neuroretinal rim tissue and some degree of peripapillary atrophy. Several clinical features, including early age of onset, preferential loss of central vision, sparing of the peripheral fields, pallor of the remaining neuroretinal rim, and a family history of unexplained visual loss or optic atrophy, help distinguish patients with DOA from those with NTG.

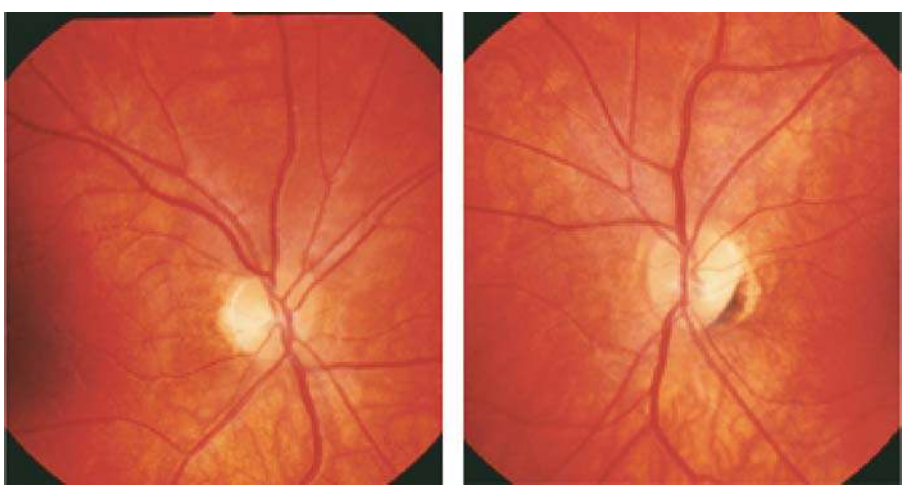

FIGURE 7.2. Autosomal dominant optic atrophy. Both optic discs reveal temporal pallor. Visual acuity is 20/60 OU with poor color vision. (Reprinted from Spalton et al.,[10] with permission from Elsevier.)

Other neurological abnormalities have occasionally been associated with DOA. Another study[89] also expands the spectrum of phenotypes associated with mutations of OPA1. An R445H mutation in the OPA1 gene results in optic atrophy, sensorineural hearing loss, ptosis, and ophthalmoplegia.

Diagnostic Testing

Genetic testing for the OPA1 gene can be performed on whole blood. MRI of the optic nerves reveals small intraorbital optic nerves and sheaths with no signal abnormality and clearly visible CSF space between the nerve and the sheath.[90] Electrophysiological testing shows a normal flash electroretinogram, absent or delayed pattern visually evoked potentials suggestive of a conduction deficit, and N95 waveform reduction on the pattern electroretinogram, consistent with a primary ganglion cell pathology.[88]

Histopathology of DOA

The site of pathology in dominant optic atrophy is thought to be the retinal ganglion cell. The outer retina appears to be normal and retinal ganglion cell loss occurs primarily in the macula and in the papillomacular bundle of the optic nerve. In one postmortem study in a 56-year-old woman by Johnston et al.,[92] marked decrease in the number of retinal ganglion cells in the macular region with a variable degree of degenerative changes were seen. Axons had variable degrees of noninflammatory demyelination. In another postmortem study of an 86-year-old man by Kjer et al.,[93] similar findings were reported and demyelination of the optic chiasm, optic tracts, and transsynaptic degeneration in the lateral geniculate body was also observed.

Pathophysiology of DOA

The pathogenic characteristics of OPA1 resemble those of LHON, which results from a defect of the mitochondrion. Mutations in the mitochondrial gene presumably lead to insufficient energy supply in the highly energy-demanding neurons of the optic nerve, especially the papillomacular bundle, and cause blindness by a compromise of axonal transport in retinal ganglion cells. Alexander et al.[94] hypothesized that mutations in the OPA1 gene affect mitochondrial integrity, resulting in an impairment of energy supply. On phosphorus magnetic resonance spectroscopy,[94] defective oxidative phosphorylation has been demonstrated in 6 OPA1 patients from two unrelated families with a 4-bp deletion in the OPA1 gene. The time constant of postexercise phosphocreatine resynthesis was significantly increased in patients compared to controls, indicating a reduced rate of mitochondrial ATP production in the patients. Similar findings have been observed in patients with LHON.

Payne et al.[90] hypothesized that although OPA1 is a nuclear gene, the fact that the gene product localizes to mitochondria suggests that mitochondrial dysfunction might be the final common pathway for many forms of syndromic and nonsyndromic optic atrophy, hearing loss, and external ophthalmoplegia. With quantitative real-time polymerase chain reaction (PCR),[95] significantly decreased levels of cellular mtDNA in blood from four of eight patients with OPA1 were found (range, 412.0 to 648.0 copies per cell) compared to controls (1148.6 ± 406.9). Three patients had decreased levels (813.2 to 1133.6), and one patient had normal levels (1455.3). The findings were consistent with the hypothesis that OPA1 gene mutations may result in decreased numbers of mitochondrial organelles by apoptosis. However, neither mtDNA content nor genotype correlated with phenotype, indicating that additional epigenetic factors are involved. It was postulated that selective damage to retinal ganglion cells in OPA1 may result from a combination of high energy requirements of retinal cells in the macular area and increased sensitivity of retinal ganglion cells to free radicals and oxidative stress.

Molecular Genetics and the Genetic Heterogeneity of DOA

DOA is an inherited mitochondrial disease such that the genetic mutation affects autosomal DNA, not mitochondrial DNA as does LHON. DOA has been linked to two different

loci in which most cases have been mapped to chromosome 3q28-qter (OPA1).[96] Only one German family has been mapped to chromosome 18q12.2–12.3 (OPA4).[97] Further genetic heterogeneity probably occurs, such as in the variant of DOA associated with sensorineural deafness that does not link to these loci.[98]

OPA1 protein comprises a highly basic amino-terminal that has a mitochondrial targeting sequence (MTS), a dynamin-GTPase domain, and C-terminus of unknown function. OPA1 is a dynamin-related protein that may be a major organizer of the mitochondrial inner membrane, contributing to cristae maintenance, mitochondrial structure, and *cytc* sequestration.[96]

There is a wide spectrum of mutations and more than 70 have been reported, including missense, nonsense, deletion/insertion, and splicing mutations.[99–101] Mutations are located throughout the gene, but three clusters most commonly occur at the leader sequence for mitochondrial import, the GTPase domain, and the –COOH terminus.[100] Because most mutations result in a truncated protein, these mutations probably represent null alleles, and dominant inheritance of the disease may result from haploinsufficiency of OPA1. Further evidence for haploinsufficiency as the predominant mechanism of the disease has been provided by the identification of a 560- to 860-kb microdeletion on chromosome 3q28 that results in the complete loss of one copy of the OPA1 gene.[102] Missense mutations are less common, are clustered in the GTPase domain, and probably lead to a loss of function of the protein and to haplotype insufficiency. A cluster of truncation mutations affect the C-terminus, and a dominant-negative effect has been hypothesized in these cases.[99] Asymptomatic carriers of OPA1 mutations have been identified within families, leading to the recalculation of a consistently lower penetrance.[101] A frameshift mutation, the 2708del (TTAG), appears to be the most frequent in Caucasian patients.[99,100]

There is wide variability in both penetrance and clinical severity, from family to family with the same mutation and from mutation to mutation. Unknown genetic or epigenetic and environmental factors may play a role in the phenotypic expression of DOA.[103]

Treatment of DOA

There is currently no effective treatment to reverse or prevent visual loss from DOA, but genetic testing for OPA1 gene and genetic counseling can help in family planning. A variety of low-vision devices are also available to patients.[104]

Normal Tension Glaucoma as a Hereditary Optic Neuropathy

NTG and DOA share overlapping clinical features. NTG may be a hereditary optic neuropathy related to mitochondrial dysfunction, as in DOA. In a study by Aung et al.,[105] an association between polymorphisms in the OPA1 gene and NTG was found. About 20% of NTG patients carried two single nucleotide polymorphisms on intervening sequence eight of the OPA1 gene compared to only 3.7% of controls. The OPA1 gene appears to be strongly associated with NTG. There may be subgroups of NTG that are distinguished by genetic variations in OPA1. Other genes may also play a role in NTG, but apolipoprotein E (APOE) allele ε4, which is linked to neuronal cell death and survival in neurodegenerative diseases, does not have a role in the pathogenesis of NTG.[106]

NTG is a chronic optic neuropathy with features of optic disc cupping and corresponding visual field defects with intraocular pressures in the normal range of usually less than 22 mmHg. Up to 20% to 50% of all cases of open-angle glaucoma may actually represent NTG.[107] In contrast to DOA, which presents early in life, usually between 4 and 8 years of age,[76] this disorder more commonly affects females around 60 years of age. It is also more prevalent in Japan in that NTG may be three times that of primary open-angle glaucoma (POAG).[108] Although DOA is an autosomal dominant disorder, no clear inheritance pattern has been established for NTG, except for a few reports of autosomal dominant pattern pedigrees.[109,110]

Decrease in visual acuity occurs when nasal peripheral defects extend into the central areas

of fixation. In the study by Levene,[111] 36% of the 53 patients had visual acuity worse than 20/40. This similar insidious progression of visual field defects leading to gradual worsening of visual acuity is also characteristic of DOA.

A blue-yellow dyschromatopsia is observed in both NTG and DOA, which can be detected on Farnsworth–Munsell 100-hue test in up to 94% of patients with DOA.[84] Only 34% to 85% of NTG patients have tritan defects.[76]

The visual field defects in NTG have been described as more localized, denser, and closer to fixation.[112] Cecocentral or paracentral scotoma may be seen in both DOA and NTG. Visual field defects nasal to fixation may be more depressed in patients with NTG than in those with high-pressure glaucoma.[112] Defects extending to within 5° of fixation are more commonly seen in NTG than in POAG.[110]

In NTG, generalized or focal enlargement of the physiological cup, nerve fiber layer loss, splinter disc hemorrhages, and focal notching of the neural rim are often seen. Superficial splinter hemorrhages appear to be more common in NTG than in POAG. In NTG, more diffuse neuroretinal rim thinning extends to the nasal aspect, whereas the temporal aspect of the disc in DOA is more affected with sparing of the nasal neuroretinal rim.[88]

Acquired pits of the optic nerve and focal areas of neuroretinal rim thinning with excavation of the lamina cribosa appear to be more common in patients with NTG compared to patients with open-angle glaucoma.[88,106]

Early treatment with the goal of reducing intraocular pressure at least 30% has been shown to be helpful in reducing progression of visual loss in only some patients because NTG has a variable course.[113] Further studies are needed on the efficacy of neuroprotective agents, such as memantine, and neurotrophic factors.[113]

Autosomal Recessive Optic Atrophy

Autosomal recessive optic atrophy is rare and presents in the first 3 years of life. In contrast to dominant optic atrophy, the visual acuity is worse than 20/200 and is associated with visual deprivation-associated nystagmus and achromatopsia or dyschromatopsia. The diffusely atrophic optic discs often have deep cupping. Peripapillary retinal arterioles are occasionally attenuated. Because autosomal recessive optic atrophy is so rare, it remains a diagnosis of exclusion. Retinal dystrophies, such as Leber congenital amaurosis and autosomal recessive cone dystrophy with optic atrophy, need to be ruled out with a thorough retinal examination and electroretinogram (ERG).[114]

X-Linked Optic Atrophy (OPA2)

Rarely do some families show a clear pattern of X-linked inheritance of optic atrophy, in which males have early-onset, progressive decrease of visual acuity. Female carriers do not show abnormalities. In a study of a family spanning three generations by Volker-Dieben et al.,[115] affected males were, in several instances at least, mentally retarded and showed mild neurological abnormalities, such as hyperactive knee jerks, absent ankle jerks, extensor plantar reflexes, dysarthria, tremor, dysdiadochokinesia, and difficulty with tandem gait. No abnormality was described in obligatory heterozygotes. In one family with a four-generation history of the disease, linkage was demonstrated to a gene located at Xp11.4-Xp11.21.[116]

Behr's Syndrome

Behr's syndrome is a rare disorder with an autosomal recessive pattern of inheritance, affecting children up to 10 years of age. Optic atrophy usually occurs in the first 8 years of life. Visual loss becomes moderate to severe, and horizontal nystagmus develops. Other systemic abnormalities also develop, including ataxia, hypertonia, pyramidal and extrapyramidal dysfunction, spastic paresis, pes cavus, mental retardation, and urinary incontinence. In most cases, abnormalities do not progress after childhood. MRI of the brain may show cerebellar

atrophy.[117] Histopathological examination may show central atrophy of the optic nerves and total disarray of the normal laminar pattern of the lateral geniculate nucleus, neuronal loss, and gliosis. Numerous axonal spheroids can also be seen.[117,118]

Wolfram Syndrome or Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy, and Deafness

Wolfram's syndrome, an autosomal recessive disorder, is also known as diabetes insipidus, diabetes mellitus, optic atrophy, and deafness (DIDMOAD), or diabetes insipidus, diabetes mellitus, optic atrophy, and sensorineural hearing loss. The gene for this disorder is located on chromosome 4p. Because of wide phenotypic variations in DIDMOAD, some patients have ataxia, hypogonadism, and psychiatric illness. The exact prevalence of this syndrome is unknown.[119,120]

Symptoms and Signs

The order of development of the clinical signs of Wolfram syndrome is variable. In general, however, insulin-dependent diabetes develops first, followed by optic atrophy and diabetes insipidus; deafness occurs later. Progressive optic atrophy is usually diagnosed before 12 years of age. Other clinical signs may appear at various ages before 25 years. Some less common features may include ptosis, anosmia, ataxia, nystagmus, seizures, mental retardation, psychiatric disorders, and hypogonadotropic hypogonadism.[121]

Visual acuity may be normal in the early stages, despite mild dyschromatopsia and optic atrophy. Visual loss then progresses to worse than 20/200. The visual field defect is most often concentric and is occasionally associated with a central scotoma. Abnormal pupillary reflexes and horizontal nystagmus have also been reported. The optic disc often has diffuse pallor with mild to moderate cupping. Pigmentary retinopathy and abnormal ERG findings have been reported in 30% of patients and diabetic retinopathy in 20%. The visual evoked potentials (VEP) to flash and checkerboard stimuli reveal reduced amplitudes.[121]

MRI of the brain may reveal diffuse atrophy and absence of hyperintensity of the posterior pituitary, indicating degeneration of the supraoptic and paraventricular nuclei of the hypothalamus.[121]

Diabetes insipidus and sensorineural hearing loss affecting high frequencies often begin in the first or second decade of life. Approximately 75% of those affected develop diabetes insipidus and about 60% develop sensorineural hearing loss. Neurogenic bladder dysfunction develops early in the third decade and multiple neurological abnormalities early in the fourth decade. About 60% have neurological complications, such as gait ataxia, seizures, startle myoclonus, depression, mental retardation, central apnea, anosmia, megaloblastic and sideroblastic anemia, ptosis, Adie's pupil, ophthalmoplegia, convergence insufficiency, vertical gaze palsy, and nystagmus.[122]

Diagnostic Testing

The diagnosis of Wolfram syndrome requires the presence of optic atrophy and juvenile-onset diabetes mellitus that cannot be explained by other causes.[122]

The diagnosis of DIDMOAD syndrome should be investigated in children who present with unexplained visual loss or with persistent polyuria and polydipsia despite adequate blood sugar control. A baseline and annual MRI of the brain, hearing test, ultrasound study of the urinary tract, and ophthalmologic examination should be performed. The differential diagnosis of optic atrophy and diabetes mellitus includes Friedrich's ataxia, Alstrom syndrome, infantile Refsum disease, and Lawrence–Moon–Biedl syndrome.[122]

Molecular Genetics and Genetic Heterogeneity of DIDMOAD

Wolfram syndrome is an autosomal recessive disorder linked to a gene located at 4p16.1.[123] The gene responsible for Wolfram syndrome, at locus WTS1, codes for "Wolfranin," a protein of uncertain function. Mutations of WTS1 may

include nonsense mutations, missense mutations, in-frame deletions, in-frame insertions, and frameshift mutations.[123] Hardy et al.[121] performed direct DNA sequencing to screen the entire coding region of the WFS1 gene in 30 patients from 19 British kindreds with Wolfram syndrome. DNA was also screened for structural rearrangements (deletions and duplications) and point mutations in mtDNA. No pathogenic mtDNA mutations were found in this cohort. The authors identified 24 mutations in the WFS1 gene: 8 nonsense mutations, 8 missense mutations, 3 in-frame deletions, 1 in-frame insertion, and 4 frameshift mutations. Of these, 23 were novel mutations, and most occurred in exon 8. Most patients were compound heterozygotes for 2 mutations, and there was no common founder mutation. No clear-cut correlations between any of the observed mutations and disease severity were found. There were no obvious mutation hotspots or clusters.

The clinical manifestations of Wolfram syndrome have some similarities with mitochondrial disease, such as those with chronic progressive ophthalmoplegia. Some patients with Wolfram syndrome also have the 11778 mtDNA mutation associated with LHON, a condition which is believed to represent the random overlap of the two disorders. Clinical manifestations from both autosomal mutations on chromosome 4p (Wolfram's syndrome) and multiple deletions in mitochondrial DNA have been observed in two studies.[123,124] In the first study, by Rotig et al.,[124] a female infant presented with insulin-dependent diabetes mellitus and then gradually had optic atrophy and sensorineural deafness, consistent with the diagnosis of Wolfram's syndrome. Her multiorgan involvement and development of mild elevated lactate represented a deficiency of the respiratory chain and a 7.6-kb heteroplasmic deletion of the mtDNA. In the second study, by Barrientos et al.,[123] four sisters whose parents were first cousins presented with insulin-dependent diabetes mellitus and dyschromatopsia followed by severe optic atrophy in their thirties. These patients initially were thought to have had Wolfram's syndrome until they later developed psychiatric abnormalities, sphincter disturbances, anosmia, walking instability, tremor, dysphagia, and swallowing difficulties. Genetic testing in the sisters showed that both nuclear and mitochondrial genomic abnormalities were present in their recessive disorder.

Type III 3-Methylglutaconic Aciduria (OPA3)

Type III 3-methylglutaconic aciduria (MGA) is a rare syndrome reported in persons of Iraqi-Jewish ancestry. The gene for type III MGA has been mapped to the long arm of chromosome 19 at 19q13.2-q13.3 or OPA3. OPA3 consists of two exons and encodes a peptide of 179 amino acid residues.[125]

Costeff et al.[126] described 19 patients with a familial syndrome consisting of infantile optic atrophy and an early-onset extrapyramidal movement disorder dominanted by chorea. About half the patients developed spastic paraparesis at 20 years of age. Mild cognitive impairment and ataxia were common. Urinary excretion of 3-methylglutaconic acid and 3-methylglutaric acid were elevated. Nine of the 10 families, including all those with multiple affected siblings, belonged to the Iraqi-Jewish community in Israel, a group with an estimated minimal prevalence rate of 1 in 10,000. The disorder had some similarities to Behr's syndrome, but the neurological aspects were distinctive.

Autosomal Dominant Progressive Optic Atrophy with Congenital Deafness

Optic atrophy and congenital sensorineural hearing loss is an autosomal dominant syndrome characterized by severe congenital deafness followed by progressive visual loss starting in the second decade. Progressive optic atrophy results in only mildly reduced visual acuity. In a case report by Kollarits et al.,[127] four members of a family had the hereditary syndrome of dominantly inherited progressive optic atrophy and congenital sensorineural deafness. Hearing evaluations revealed that two members had a potentially treatable form of deafness.

Autosomal Dominant Progressive Optic Atrophy with Progressive Deafness and Ataxia

This very rare autosomal dominant syndrome is characterized by slowly progressive bilateral optic atrophy and sensorineural hearing loss with an onset between 2.5 and 9 years of age.[128] This syndrome also includes ataxia and may be different or related to Friedreich's ataxia.[128]

Hereditary Optic Atrophy with Progressive Deafness and Polyneuropathy

Hereditary optic atrophy with progressive deafness and polyneuropathy may be inherited as an autosomal dominant, autosomal recessive, or X-linked form. Hagemoser et al.[129] reported two unrelated families with a disorder characterized by optic atrophy, hearing loss, and peripheral neuropathy. In the first family, 13 affected members spanning four generations had male-to-male transmission of the disorder. Most patients developed bilateral hearing loss and visual loss with optic atrophy by 5 to 6 years of age. Neurological features were only seen in a subset of patients as adults, and consisted mainly of decreased vibratory sensation and lower extremity hyporeflexia. Nerve conduction velocities suggested an axonal sensory and motor neuropathy. The second family had three affected members over three generations. Optic atrophy was seen by 10 years of age. The proband had visual loss by 5 years of age and hearing loss by 13 years. Sensory ataxia developed during adulthood. Therefore, it was concluded that this disorder showed autosomal dominant inheritance with initial presentation of optic atrophy followed by deafness and ataxia.

Hereditary optic atrophy with progressive deafness and polyneuropathy may be inherited in an autosomal recessive form. In a report by Iwashita et al.,[130] a Korean brother and sister developed optic atrophy, hearing loss, and distal neurogenic atrophy. The older brother, who was more severely affected, showed bilateral ulnar deviation and flexed fingers at 8 years of age. At 13, he developed progressive optic atrophy and hearing loss. At 25, his lower extremities had severe atrophy and sensory loss in all modalities. He had an ataxic, broad-based gait. Nerve conduction velocities were normal, and sural nerve biopsy showed slight demyelination. The sister had distal weakness and atrophy of the upper limbs with the same hand deformity as her brother, but no weakness or atrophy of the lower limbs. She had mild optic atrophy and hearing loss. She had no sensory impairment.

The X-linked form of hereditary optic atrophy with progressive deafness and polyneuropathy is represented by X-linked Charcot–Marie–Tooth disease. The locus of this gene is CMTX5 on chromosome Xq21.32-q24.[130] Few case reports describe the phenotype of this disorder. In a report by Rosenberg and Chutorian,[131] two brothers developed early-onset hearing loss, lower extremity weakness and atrophy during childhood, and progressive optic atrophy at about 20 years of age. The older brother had pes cavus, and both brothers required a cane for walking by 15 years of age. As adults, both had severe distal weakness and atrophy in all extremities, with broad-based gait and atrophy of the intrinsic hand muscles. They had a sensorimotor peripheral neuropathy. A 3-year-old nephew showed a similar phenotype. Later evidence suggested that the mother, grandmother, and great-grandmother of the affected nephew also had slowly progressive hearing loss, suggesting X-linked semidominant inheritance. In another report by Kim et al.,[132] a Korean family had six males who had early-onset hearing loss, decreased visual acuity, and motor impairment in an X-linked recessive pattern of inheritance. Bilateral profound sensorineural hearing loss was present at an early age. They had progressive lower extremity weakness by 10 to 12 years of age. All developed bilateral progressive visual failure starting at 8 to 13 years of age. The proband had bilateral optic disc pallor and abnormal visual evoked potentials consistent with an optic neuropathy. Obligate female carriers were unaffected. The phenotype of the affected males in

this family resembled that described in the previous study by Rosenberg and Chutorian.[131]

Autosomal Recessive Optic Atrophy with Progressive Hearing Loss, Spastic Quadriplegia, Dementia, and Death (Opticocochleodentate Degeneration)

This rare autosomal recessive syndrome is characterized by severe progressive optic atrophy, severe hearing loss, and worsening spastic quadriplegia beginning in infancy. Dementia ensues and death occurs in late childhood. Muller and Zeman[133] reported two brothers with degeneration of the optic, cochlear, dentate, and medial lemniscal systems. They developed severe optic atrophy, deafness, little or no speech, and spasticity; both died before age 10.

Opticoacoustic Nerve Atrophy with Dementia

This rare X-linked recessive disorder is characterized by initial severe sensorineural hearing loss during infancy followed by progressive optic atrophy by 20 to 30 years of age. Progressive dementia then develops in adulthood. This disorder is caused by a mutation in the TIMM8A gene at Xq22. In a report by Jensen et al.,[134] a 3-year-old boy and his two maternal uncles, aged 33 and 41 years, presented with profound sensorineural hearing loss that started during infancy. They then developed progressive optic atrophy during their teenage years, followed by progressive dementia during later adulthood. Both uncles died at the age of about 40 years. Postmortem findings revealed extensive calcification in all parts of the central nervous system, especially the meninges, blood vessels, and neurons. Calcification was thought to be secondary to degenerative changes. Skeletal muscles had moderate diffuse atrophy. Therefore, opticoacoustic nerve atrophy with dementia appears to be an X-linked neurodegenerative disorder.[134,135]

Fatal X-Linked Optic Atrophy, Ataxia, and Deafness

This X-linked recessive disorder begins with early-onset hypotonia, ataxia, vulnerability to infections, especially of the upper respiratory tract, deafness, and, later, a flaccid tetraplegia and areflexia. Death usually occurs during early childhood. The locus of the gene is Xq21.33-q24, which encodes a proteolipid protein in myelin of the central nervous system.[136] Few case reports illustrate the clinical features of this disorder. In a report by Arts et al.,[137] 12 boys in three generations of a kindred developed early-onset hypotonia, ataxia, and liability to infections. Although 1 boy was still alive at the age of 12 years, 11 had died before the age of 5 years. The surviving boy required ventilation at night and was nearly blind because of optic atrophy. On autopsy of 1 boy, almost complete absence of myelin in the posterior columns of the spinal cord was found. The female carriers had only hearing impairment in early adulthood. In another study by Kremer et al.,[136] linkage analysis was performed in a family reported by Arts et al.[137] They noted that infections were the cause of death before 6 years of age in 11 of the 12 boys. The oldest boy at 6 years of age had become nearly blind from optic atrophy and demented. Sensorimotor deficits reflected impairment of the posterior columns and the second and eighth cranial nerves and/or nuclei.

Progressive Encephalopathy with Edema, Hypsarrhythmia, and Optic Atrophy Syndrome

This autosomal dominant disorder is a progressive encephalopathy presenting in the first 6 months of infancy, followed by severe hypotonia, seizures with hypsarrhythmia, profound

mental retardation, microcephaly, hyperreflexia, extremity edema, and facial anomalies. Optic atrophy and nystagmus often develops by 10 to 20 years of age. In a report by Salonen et al.,[138] 14 patients, from 11 families, who had this syndrome had no identifiable metabolic defect that could explain the clinical features. Neuropathological findings for 8 of these patients revealed diffuse cerebral and particularly cerebellar atrophy. Cerebellar hypoplasia was considered a cardinal diagnostic feature of encephalopathy with edema, hypsarrhythmia, and optic atrophy (PEHO) syndrome.[139] Neuronal loss was severe in the inner granular layer of the cerebellum. The Purkinje cells were relatively preserved in number but were small and deformed.

Optic Neuropathy in Hereditary Ataxias

Friedreich's Ataxia

Friedreich's ataxia (FA) is the most common of the autosomal recessive spinocerebellar ataxias and accounts for at least half of the hereditary ataxias in most large case series reported.[140] The prevalence of FA is estimated to be between 1 in 22,000 to 2 in 100,000 internationally and slightly higher in Quebec. It affects mostly Caucasians and almost always presents before 20 years of age. Males and females are equally affected.[140]

Clinical Features of FA

In a clinical and genetic study of 90 families by Harding,[141] the onset of symptoms was before the age of 25 years (mean, 10.52 years) in all the index cases. In early cases of FA, limb and truncal ataxia and absent tendon reflexes in the legs appeared to be the only consistent diagnostic criteria within 5 years of presentation. Dysarthria, signs of pyramidal tract dysfunction in the legs, and loss of joint position and vibration sense were not necessarily present during the first 5 years of symptoms, but appeared to develop eventually in all cases. Visual acuity rarely was affected, but optic atrophy occured in 25% of patients with FA and resulted in occasional blindness. VEP were abnormal in two-thirds of patients, typically displaying reduced amplitude and delayed latency.[141,142] Nystagmus was observed in approximately 20% of patients with FA, but extraocular movements were nearly always abnormal, with abnormal smooth pursuit, dysmetric saccades, square wave jerks, and failure of fixation and suppression of the vestibulo-ocular reflex. Significant sensorineural deafness occured in 10% of persons with FA. About 10% of patients with FA have diabetes mellitus, which appeared to be associated with a higher incidence of optic atrophy and deafness. Cardiac abnormalities were found in more than 75% of patients. Clinical evidence of ventricular hypertrophy, systolic ejection murmurs, and third or fourth heart sounds were observed.[141,143] This gradual progressive disorder lead to the inability to walk at about 25 years of age. Ninety-five percent became wheelchair bound by the age of 44 years.

Molecular Genetics of FA

Classic FA is an autosomal recessive disorder caused by a gene mutation at the centromeric region of chromosome 9 (9q13–21.1) at the site of the gene encoding for the 210-amino-acid protein frataxin.[144,145] This mutation is characterized by an excessive number of repeats of the GAA (guanine adenine adenine) trinucleotide DNA sequence in the first intron of the gene coding for frataxin.[144] It is the only disease known to be the result of a GAA trinucleotide repeat. This expansion alters the expression of the gene, decreasing the synthesis of frataxin protein. The expanded GAA repeat is thought to result in frataxin deficiency by interfering with transcription of the gene by adopting an unstable helical structure.[145] The larger the number of repeats, the more profound is the reduction in frataxin expression. Variability in the clinical presentation of FA may be explained by the extent of this trinucleotide repeat expansion. The age of disease onset, its severity, rate of progression, and extent of neurological involvement vary with the number of repetitive GAA sequences. Larger GAA expansions correlated with earlier age of onset and shorter times to loss of ambulation.[145]

Point mutations not only reduce levels of the frataxin protein but are also responsible for the creation of abnormal protein. They also represent another source of variability in the clinical presentation of FA.[146] Seventeen different point mutations have so far been described in FA.[146] Between 1% and 5% of the point mutations are single base changes in the sequence of the FA gene causing missense, nonsense, or splicing mutations. Patients with missense mutations have either mild or severe symptoms, whereas those with splicing, nonsense, and initiation codon mutations, which are associated with nonfunctional frataxin, have a severe phenotype.[146] Point mutations of the frataxin gene involving the amino-terminal typically present with a more benign course than those of the carboxy-terminal. The three most common point mutations include the Il54F mutation among southern Italians, the ATG to ATT mutation of the start codon, and the G130V mutation. Patients with the G130V mutation tend to have slower disease progression.[146]

Pathophysiology of FA

Cells and tissues of the body are differentially sensitive to frataxin deficiency. Cells normally requiring and producing greater amounts of frataxin tend to be most affected by FA.[147] For example, sensory neurons in the dorsal root ganglion express the frataxin gene and are affected greatly in FA. Frataxin has been shown to be essential for normal mitochondrial function, both for oxidative phosphorylation and for iron homeostasis.[148] Strong evidence supports that frataxin deficiency results in iron accumulation within mitochondria of affected cells in cell culture lines. The excessive mitochondrial accumulation of iron affects cytosolic iron levels. Excess intracellular iron stimulates the increased generation of free radicals and mitochondrial damage. Iron excess inactivates mitochondrial enzymes essential for the production of ATP. Cell death, particularly of neurons of the spinal cord and peripheral nervous system, ensues.[147]

On histological cross section through the lower cervical cord, loss of myelinated fibers of the dorsal columns, corticospinal tracts, and some of the spinocerebellar tract may be seen. The affected tracts have compact fibrillary gliosis but no breakdown products or macrophages because of the very slow rate of fiber degeneration. The dorsal spinal root ganglia show shrinkage and eventual disappearance of neurons associated with proliferation of capsular cells. The posterior roots are nearly devoid of large myelinated fibers. Neuronal degeneration is seen in Clarke's column within the thoracic spinal cord, brainstem (cranial nerve nuclei VIII, X, and XII), and cerebellum (dentate nucleus and the Purkinje cells of the superior vermis).[147]

Diagnosis of FA

The diagnosis of FA essentially is a clinical one. A specific trinucleotide repeat expansion assay is available commercially in the United States and should be performed in all suspected cases of FA.[140] The CSF abnormality is usually normal in patients with FA. MRI of the brain and spinal cord in patients with FA often reveals atrophy of the cervical spinal cord with minimal evidence of cerebellar atrophy.[140] On echocardiogram hypertrophic cardiomyopathy is present in approximately 40% of patients. The severity of left ventricular hypertrophy is related to the number of GAA repeats. The electrocardiogram is abnormal in approximately two-thirds of patients, with widespread T-wave inversion.[141] Nerve conduction velocity study findings in FA usually are normal or reveal only mildly reduced velocities. Visual evoked potentials are abnormal in two-thirds of patients with FA. Absent or delayed latency and reduced amplitude of the P100 wave are seen.[142] Brainstem auditory evoked responses are typically abnormal in FA, displaying absent waves III and IV with preservation of wave I. Somatosensory evoked potentials reveal delayed, dispersed potentials at the sensory cortex, as well as abnormal central motor conduction.[140]

Management of FA

No effective therapy to delay the progression of FA is yet available. Free radical scavengers and antioxidants (e.g., coenzyme Q,

N-acetylcysteine, vitamin E) currently are being considered for treatment trials. Iron chelation therapy may also be a possibility.[148]

Spinocerebellar Ataxia Type 1

Spinocerebellar ataxia type 1 (SCA-1) is an autosomal dominant disorder caused by a gene mutation that is an expanded CAG repeat on chromosome 6p22-p23. The triplet nucleotides are expanded from 42 to 82 repeats compared to the normal 19 to 36 CAG repeats.[149] This mutation involves a gain of function resulting in a protein, ataxin-1. Age of onset and severity of the disease depend upon the length of the CAG expansion. A longer expansion of the trinucleotide repeat is correlated with an earlier onset and more severe presentation of the disease. Anticipation, or amplification of the CAG repeats with each successive generation, also occurs.[149]

The onset of clinical symptoms and signs is usually at 40 years of age. Gait and extremity ataxia, dysarthria, and bulbar dysfunction are followed by loss in vibration and proprioception. Pyramidal tract signs, optic atrophy, and dysphagia are more frequent in SCA-1 than in SCA-2 and SCA-3 patients.[150] In contrast to SCA-2, in which optic atrophy is secondary to retinal degeneration, up to 30% of patients with SCA-1 have primary optic atrophy. The severity of this optic atrophy varies among patients, and visual acuity is not severely impaired.[150] Oculomotor disorders are also seen in most patients, including impaired smooth pursuit and optokinetic nystagmus, gaze-evoked nystagmus, supranuclear ophthalmoplegia, and lid retraction.[151] Facial palsy, bulbar symptoms, and extrapyramidal features, such as dystonia and chorea, develop later in the disease.[150]

The exact pathophysiological mechanisms underlying SCA-1 are not yet entirely understood. On histopathology, degeneration of Purkinje cells, dentate nucleus, inferior olive, red nucleus, and cranial nerve nuclei III, X, and XII are often seen. Occasionally, the substantia nigra, putamen, pallidum, and subthalamic nucleus are also affected.[152,153]

MRI of the brain reveals mild olivopontocerebellar atrophy, less severe than that in SCA-2 and olivopontocerebellar atrophy (OPCA) patients.[153] Definitive diagnosis of SCA-1 is based upon demonstration of an expanded CAG repeat on chromosome 6p22-p23.[150]

Low vision, occupational, speech, and physical therapy can be offered to improve or maintain patients' functional capacities and help them adapt to their limitations.[150]

Optic Neuropathy in Hereditary Polyneuropathies

X-Linked CMT

See earlier section on hereditary optic atrophy with progressive deafness and polyneuropathy.

Hereditary Motor and Sensory Neuropathy VI with Optic Atrophy

Hereditary motor and sensory neuropathy type VI (HSMN6) is an autosomal dominant disorder that presents with visual loss starting at 7 to 10 years of age.[155] As patients with HMSN6 develop optic atrophy, decreased visual acuity occurs in the twentieth decade and worsens to light perception only by age 30. An axonal sensory-motor polyneuropathy that may be associated with peroneal muscular atrophy also develops in early childhood, causing gait difficulties.[155]

Phenotypic variability occurs in the neurological and ophthalmologic features of HSMN6. In a study by Voo et al.,[156] 58 members of a family were affected by autosomal dominant HMSN6. Twelve had both peripheral neuropathy and optic atrophy; 3 others had either neuropathy or optic atrophy. Although there was clinical variability, most had childhood onset of progressive visual loss caused by optic atrophy, abnormal gait, distal sensory impairment, and hyporeflexia. Other variable features included hearing loss, tinnitus, cogwheel ocular pursuit, and anosmia. Incomplete penetrance was observed. In another report by Zuchner et al.,[157] 10 affected patients from six unrelated families

had inherited HMSN6 as an autosomal dominant disorder. All had an early onset of a severe axonal peripheral neuropathy starting at about 2 years of age. Optic atrophy began later at about 19 years of age. Most experienced subacute loss of visual acuity with color defects, central scotoma, and pale optic discs. Sixty percent of the patients experienced significant recovery of their visual acuity after several years. The mechanism involved in this visual recovery is not yet fully understood.

Hereditary Sensory and Autonomic Neuropathy Type III or Familial Dysautonomia

Hereditary sensory and autonomic neuropathy type III (HSAN3), or familial dysautonomia (FD), can be caused by mutations in the IKBKAP gene on chromosome 9q31-q33.[158] It is an autosomal recessive disorder occurring almost exclusively in persons of Ashkenazi Jewish descent.[159] Neuropathological findings reveal that the mean volumes of the superior cervical sympathetic ganglion and the preganglionic neurons in the first three thoracic cord segments are characteristically reduced by about 30% to 50%.[160]

The criteria for the diagnosis of HSAN3 require the following five signs: (1) lack of axon flare after intradermal injection of histamine, (2) absence of fungiform papillae on the tongue, (3) miosis of the pupil after conjunctival instillation of methacholine chloride (2.5%), (4) absent deep tendon reflexes, and (5) diminished tear flow.[159] However, consistent neuropathological findings in sural nerve biopsies may be the best diagnostic criterion to differentiate familial dysautonomia from other forms of congenital sensory neuropathy.[161]

Only a few case reports illustrate the neuroophthalmic features associated with this disorder. In a report by Rizzo et al.,[162] patients with HSAN3 presented with optic atrophy after 10 years of age. Although optic atrophy appears to be an uncommon finding, the increasing life span of patients with HSAN3 could increase the probability of identifying optic atrophy in the future. Groom et al.[163] described a patient with familial dysautonomia who presented with an optic neuropathy and chiasmal visual field defects.[162] Schnitzler et al.[164] described a 21-year-old woman who presented with a slowly progressive tetraparesis, bilateral optic atrophy, and dysautonomia since early childhood. Although the autonomic, motor, and visual symptoms and signs resembled familial dysautonomia, some hallmarks of familial dysautonomia were absent, such as absence of fungiform papillae of the tongue, abnormal reaction on intradermal histamine injection, and absent tendon reflexes. It was suggested that the progressive bilateral optic atrophy, tetraparesis, and dysautonomia could all be a variant of familial dysautonomia.

Optic Neuropathies in Neurodegenerative Disorders of Childhood

Mucopolysaccharidoses with Optic Neuropathy

Mucopolysacaridoses (MPS) is an abnormal storage disease caused by a deficiency of the lysosomal enzymes that catalyze the degradation of glycosaminoglycans. Mucopolysaccharides are stored in the cornea, connective tissue, bone, cartilage, and reticuloendothelial system. MPS IH (Hurler), MPS IS (Scheie), MPS IHS (Hurler–Scheie), MPS IIA and IIB (Hunter), MPS IIIA and IIIB (Sanfilippo), MPS IV (Morquio), and MPS VI (Maroteaux–Lamy) are all autosomal recessive diseases, except for type II, which is X linked.[165]

In the various phenotypes of the mucopolysaccharidoses, meningeal deposition may lead to decreased CSF absorption and increased intracranial pressure causing eventual optic atrophy. Local compression of the optic nerve can be caused by meningeal or scleral mucopolysaccharide deposition. Accumulation of mucopolysaccharides within glial cells of the optic nerve has also been observed.[166] Corneal clouding and retinal degeneration commonly occur in MPS I.[165] Other systemic features involve the brain, visceral organs, connective

tissue, and bone. For example, abdominal hernia, dysostosis multiplex, stiff joints, visceromegaly, and mental retardation can be observed in the Hurler (MPS IH) phenotype.[165]

Definitive diagnosis is established by alpha-L-iduronidase enzyme assay using artificial substrates (fluorogenic or chromogenic) in cultured fibroblasts or isolated leukocytes.[167]

Allogeneic bone marrow transplantation before the age of 2 years prevents disease progression in Hurler syndrome and prolongs life. Because allogeneic bone marrow transplantation is not available to all patients, gene therapy may offer effective treatment for patients with Hurler syndrome without a matched sibling donor. In a study by Fairbairn et al.,[168] a retroviral vector carrying the full-length cDNA for alpha-L-iduronidase was used to transduce bone marrow from patients with this disorder. The gene was then transferred into primitive CD34+ cells and subsequently expressed the enzyme in their maturing progeny. The efficiency of gene transfer, as assessed by PCR analysis of hematopoietic colonies, was about 25% to 56%. The enzyme was then secreted into the medium, and functional localization was demonstrated by reversal of the phenotypic effects of lysosomal storage in macrophages.

Lipidoses with Optic Neuropathy

The lipidoses are lysosomal enzyme storage diseases that are autosomal recessive. Mental and motor retardation is common to infantile and juvenile GM_1 gangliosidosis (GM_1-1 and GM_2-2), GM_2 gangliosidosis (Tay–Sachs disease, Sandhoff disease, and late infantile, juvenile, and adult GM_2 gangliosidosis), and the infantile form of Neimann–Pick disease.[169]

Tay-Sachs disease is an autosomal recessive, progressive neurodegenerative disorder that localizes to chromosome 15q23-q24.[169] The majority of the patients are infants with the Tay–Sachs form of the disease associated with a severe deficiency of beta-*N*-acetylhexosaminidase A (hexosaminidase A). Both hexosaminidase A and B are deficient in Sandhoff disease. Classic Tay–Sachs disease begins with early developmental psychomotor retardation, followed by paralysis, blindness, exaggerated startle response to acoustic stimuli, and seizures. On funduscopy, lipid-laden ganglion cells form a gray-white area around the retinal fovea centralis, leaving a central "cherry-red" spot. Optic atrophy is also typically observed.[169]

Definitive diagnosis of Tay–Sachs disease is established by showing the deficiency of hexosaminidase A in leukocytes or cultured fibroblasts. Amniocentesis to detect this disorder is available. Treatment is supportive.[169]

Gray Matter Neurodegenerative Disorders with Optic Atrophy

Infantile Neuroaxonal Dystrophy

Infantile neuroaxonal dystrophy is an autosomal recessive disorder that results from a mutation in the PLA2G6 gene located on chromosome 22q12.3-q13.2.[170]

This disorder is caused by the formation of neuroaxonal spheroids in axon terminals of the central nervous system (CNS) and peripheral nervous system (PNS).[171] Swollen eosinophilic spheroids throughout the gray matter lead to cerebral degeneration. This progressive disorder usually begins within the first 2 years of life with psychomotor deterioration, bilateral pyramidal tract signs, marked hypotonia, and early visual disturbances. VEPs are abnormal. The EEG often reveals high voltage and fast rhythms, and the EMG results are consistent with chronic denervation. T_2-weighted MRI can reveal cerebellar atrophy with signal hyperintensity in the cerebellar cortex. In a report by Farina et al.,[171] a thin optic chiasm was observed on MRI in four patients with infantile neuroaxonal dystrophy.

Both clinical and pathological features are necessary for the definitive diagnosis. Pathological diagnosis requires demonstrating neuroaxonal spheroids in peripheral nerve endings of the skin or conjunctiva. Treatment is supportive.[172]

White Matter Neurodegenerative Disorders with Optic Atrophy

Adrenoleukodystrophy

Adrenoleukodystrophy is an X-linked disorder that is secondary to a mutation in the ABCD1

gene, an ATPase-binding cassette protein.[173] This mutation causes a deficiency of peroxisomal acyl coenzyme A synthetase that leads to the accumulation of the saturated very long chain fatty acids. This disorder manifests primarily in the adrenal cortex, the myelin of the CNS, and the Leydig cells of the testes.[173]

Boys are usually affected starting at the age of 7 years. Seizures and behavioral problems, including inattention, hyperactivity, and emotional lability, develop early. Visual and auditory deterioration, and motor incoordination, then develop rapidly. Periventricular demyelination, especially in the posterior cerebral hemisphere, contributes to visual loss. As demyelination affects the anterior pathways, optic atrophy becomes more apparent. MRI reveals symmetric involvement of the posterior parietooccipital white matter in 85% of patients, frontal involvement in 10%, and an asymmetric pattern in the remainder.[174]

The diagnosis is established by measuring elevated levels of very long chain fatty acids in serum.[175]

Asymptomatic individuals with the adrenomyeloneuropathy gene, as well as patients with this disorder and heterozygotes, may benefit from a combined oleic acid, VLCFA-restricted diet.[176] In a report by Aubourg et al.,[177] reversal of early neurological and neuroradiologic features was achieved in an 8-year-old boy who received bone marrow transplantation (BMT) from his fraternal twin brother. Malm et al.[178] described experience with bone marrow transplantation in three children with ALD. They concluded that BMT must be considered very early, even in a child without symptoms but with signs of demyelination on MRI, if a suitable donor is available.

Metachromatic Leukodystrophy

Metachromatic leukodystrophy is an autosomal recessive disorder caused by a deficiency of arylsulfatase A.[179] The progressive subcortical demyelination, mostly in the posterior cerebral white matter, causes dementia and blindness. Up to 50% of patients with juvenile and adult forms have optic atrophy.[179] Histopathological studies in the infantile form of metachromatic leukodystrophy have shown storage of metachromatic complex lipids in the optic nerve, retinal ganglion cells, and the ciliary nerves. Abnormal myelin metabolism also leads to peripheral demyelination causing weakness, spasticity, and ataxia.[180]

Diagnosis is established by showing the absence of arylsulfatase A in leukocytes.[180]

Bone marrow transplantation may be a treatment option. Improvement in neurodevelopmental milestones was observed[181] in a boy with late infantile metachromatic leukodystrophy after receiving a bone marrow transplant from an HLA-identical sister.[182] Improvement in neurophysiological function and sulfatide metabolism was also reported in an affected 10-year-old girl who had received a bone marrow transplant 5 years previously.

Krabbe Disease (Globoid Cell Leukodystrophy)

Krabbe disease is an autosomal recessive disorder localized to chromosome 14.[183] This progressive demyelinating disease is caused by a deficiency of galactosylceramide-β-galactosidase. Abnormal storage of galactosylceramide is seen as periodic acid–Schiff (PAS)-positive material extracellularly and cerithin in microglial cells, which later appear as globoid cells in the white matter of the CNS.[184]

Diffuse demyelination of the brain, including the entire visual pathway, and of the peripheral nerves leads to blindness and psychomotor retardation in infancy. The optic neuropathy is more severe in the early-onset phenotype.[183] In neurophysiological studies by Husain et al.[185] of 20 patients with early-onset Krabbe disease, 53% had abnormal flash VEPs compared to 6 patients with late-onset Krabbe disease who had normal flash VEPs. The abnormalities correlated well with disease severity as measured by MRI.

Diagnosis is established by showing the deficiency of glactosylceramide-β-galactosidase in leukocytes or cultured fibroblasts.[184]

Bone marrow transplantation may be a treatment option. CNS manifestations of Krabbe disease can be reversed or prevented by allogeneic hematopoietic stem cell transplantation.[185] In a study by Krivit et al.,[186] five children with Krabbe disease, one with the infantile type and

four with late-onset disease, were treated with allogeneic hematopoietic stem cell transplantation. Four of the patients had clinical CNS abnormalities before transplantation. In all four cases, CNS deterioration was reversed. In the patient with the infantile form of the disease, the expected decline in CNS function had not occurred by the age of 16 months or 14 months posttransplantation.

Pelizaeus–Merzbacher Disease

Pelizaeus–Merzbacher disease is an X-linked demyelinating disorder caused by a mutation in the gene encoding proteolipid protein-1, leading to the defective synthesis of a proteolipid protein required in the myelin sheath. In the classic type of Pelizaeus–Merzbacher disease, demyelination of the cerebral hemispheres leads to the initial signs of nystagmoid eye movement and jerking and rolling head movements or head tremor. As nystagmus disappears, dementia, choreoathetosis, ataxia, and spasticity develop. Optic atrophy occurs late in the disease.[187]

Diagnosis is established by showing the deletion of the exon coding the proteolipid protein on chromosome Xq22. MRI may be a suitable means for carrier detection. In obligate carriers, bilateral multiple areas with signal hyperintensity in the periventricular and subcortical white matter have been demonstrated.[188]

Treatment is supportive.[187]

Canavan's Syndrome

Canavan's disease is an autosomal recessive disorder caused by a point mutation in the ASPA gene mutation on chromosome 17pter-p13.[189] This mutation causes a deficiency of aspartoacylase, leading to spongy degeneration of the white matter, swollen astrocytes, and normal neurons.[190] It is thought that the dysmyelination may result from failure of *N*-acetylaspartate to serve as a carrier of acetyl groups from mitochondria to the cytosol for lipogenesis.[190] A diffuse symmetric leukoencephalopathy develops before the manifestation of psychomotor retardation. In early infancy, hypotonia, hyperextension of legs and flexion of arms, blindness, severe cognitive delay, and megalencephaly develop. Optic atrophy is prominent at 6 to 10 months of age. Death occurs at about 18 months of age.[190,191]

Diagnosis is established by showing abnormal excretion of *N*-acetyl aspartate in the urine and showing a decreased level of aspartoacylase activity in culture fibroblasts.[191] MRI often reveals diffuse leukodystrophy and high signal lesions in the globi pallidi on T_2-weighted images. MRS of the brain shows an elevated ratio of NAA/phosphocreatin + creatin (Cr) whereas the ratio of Cholin/Cr is reduced.[191]

Treatment is supportive.[191]

Other Hereditary Syndromes Associated with a Secondary Optic Atrophy

Other hereditary syndromes that have been associated with a retinal degeneration and secondary optic atrophy include neuronal ceroid lipofuscinosis, Hallervorden–Spatz disease, Menke's syndrome, Cockayne syndrome, and Leigh's syndrome.[193]

Congenital Anomalies/Mental Retardation Syndrome with Optic Atrophy

Smith–Lemli–Opitz Syndrome

Smith–Lemli–Opitz syndrome (SLOS) is an autosomal recessive inborn error of metabolism caused by a deficiency of 3-beta-hydroxysterol-delta 7-reductase, the final enzyme in the sterol synthetic pathway that converts 7-dehydrocholesterol to cholesterol.[194] The gene for this deficient enzyme maps to chromosome 11q12.13.[195] The prevalence of SLOS is about 1 in 20,000 to 60,000 births in Caucasians in the United States.

The syndrome consists of intrauterine growth retardation and multiple congenital anomalies affecting the brain, heart, eyes, face, and lungs. Visual loss may occur from optic nerve

abnormalities and cataracts. In a study of eight patients with SLOS by Atchaneeyasakul et al.,[196] optic atrophy was seen in one patient and optic nerve hypoplasia was seen in another, but the most common ophthalmologic abnormality was blepharoptosis, which was seen in six of the eight patients. Sterol analysis from ocular tissues of an aborted fetus with SLOS showed increased 7- and 8-dehydrocholesterol and a low cholesterol concentration in the retinal pigment epithelium, lens, cornea, and sclera.

It is still unclear how defective cholesterol synthesis can cause congenital malformations.[194] Diagnosis is based on demonstration of elevated levels of 7-dehydrocholesterol-delta 7-reductase in the blood or on cultured fibroblasts.[194] Mortality from spontaneous abortion and multiorgan failure in the first several weeks of life is not uncommon. Otherwise, survival depends on long-term cholesterol supplementation.[197]

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8
Congenital Disc Anomalies

Jane W. Chan

Congenital Anomalous Disc Size

Optic Nerve Hypoplasia

Optic nerve hypoplasia is the most common congenital optic disc anomaly and is a common cause of congenital blindness. The increased prevalence of this disorder reflects its greater recognition by ophthalmologists and possibly the increased incidence of alcohol and drug abuse. It may be unilateral or bilateral, and may occur with or without any associated neurological or ocular abnormalities.[1]

Optic nerve hypoplasia is an abnormally small optic nerve head that may appear gray or pale because of a decreased number of optic nerve axons with normal glial tissue.[2] The optic disc is surrounded by a yellowish peripapillary ring of sclera and an outer concentric ring of hyper- or hypopigmentation, known as the "double-ring" sign. The outer ring is located at the normal junction between the sclera and lamina cribosa. The inner ring represents the abnormal extension of retina and pigment epithelium into the outer aspects of the lamina cribosa. The surrounding large retinal veins are usually tortuous (Figure 8.1).[2–4]

The diagnosis of optic nerve hypoplasia is based upon small optic discs, decreased or normal vision, and visual field defects with corresponding nerve fiber bundle defects. Visual acuity ranges from 20/20 to no light perception. Localized defects with peripheral constriction are common. Visual acuity is determined mainly by the integrity of the papillomacular bundle and does not correlate with the size of the optic disc.[5,6]

Astigmatism is associated with optic nerve hypoplasia.[7] Visual evoked potentials (VEP) may be normal or abnormal. Unilateral or bilateral optic nerve hypoplasia may be associated with central nervous system (CNS) malformations,[8] especially forebrain malformations and endocrinological abnormalities,[9] as in septo-optic dysplasia (de Morsier syndrome) (Figure 8.2).[4] Focal thinning or absence of the side of the chiasm corresponding to the hypoplastic optic disc can be seen on magnetic resonance imaging (MRI). In bilateral optic nerve hypoplasia, the optic chiasm is atrophied. The prechiasmatic intracranial optic nerve corresponding to the hypoplastic disc is thinned. The diagnosis of optic nerve hypoplasia may be presumed based upon diminished intracranial optic nerves with other neuroradiologic features of septo-optic dysplasia.[10]

Other CNS malformations associated with optic nerve hypoplasia include abnormalities in the cerebral hemispheres and the pituitary infundibulum.[1,9] Hemispheric migration abnormalities, such as schizencephaly and cortical heterotopia, and hemispheric injury, such as periventricular leukomalacia and encephalomalacia, may occur in 45% of patients with optic nerve hypoplasia.[9] Fifteen percent of patients with optic nerve hypoplasia may have perinatal injury of the pituitary infundibulum leading to necrosis. This brain abnormality is seen as posterior pituitary ectopia on MRI, in

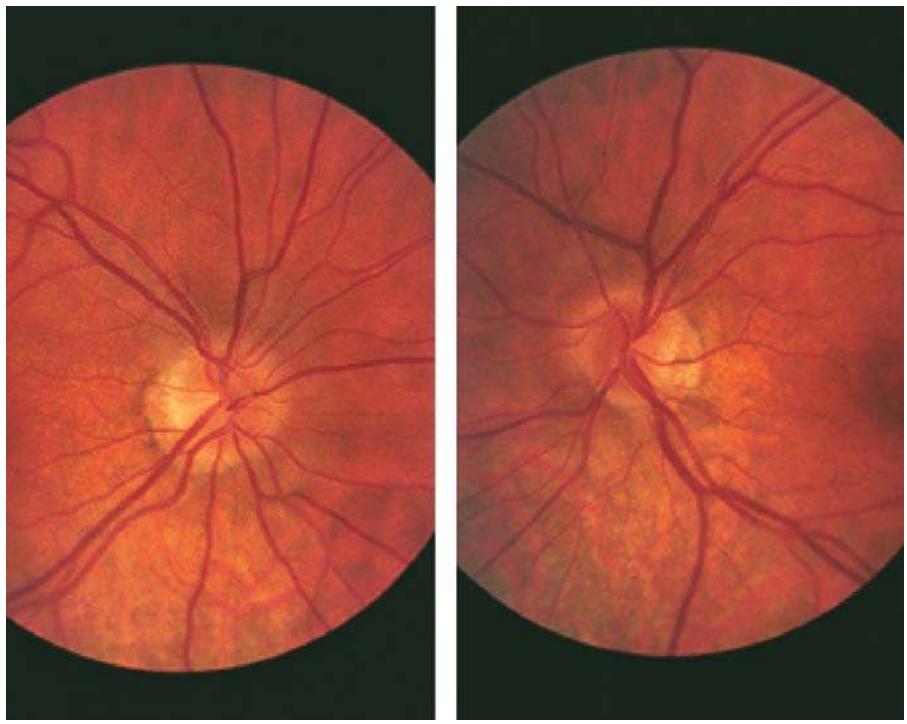

FIGURE 8.1. Optic disc hypoplasia. Both optic discs are small. The left disc (*right*) is smaller and is slightly tilted. Crowding of nerve fibers is seen nasally on both optic discs, mimicking swelling. The retinal and scleral edges can be seen in the temporal aspects of both discs. (Reprinted from Spalton et al.,[4] with permission from Elsevier.)

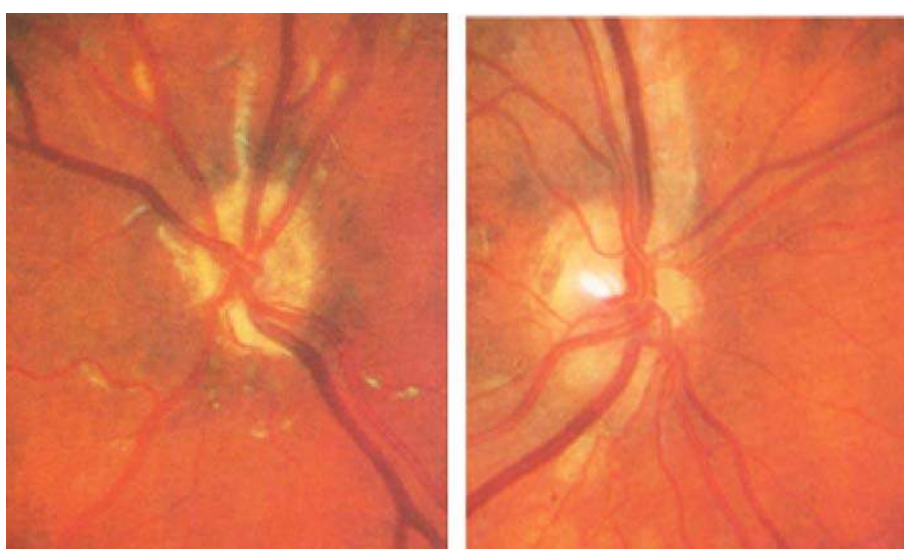

FIGURE 8.2. Optic nerve hypoplasia in septo-optic dysplasia syndrome. The right optic disc (*right*) is very small with few nerve fibers. The left optic disc (*left*) is small with almost no nerve fibers. Visual acuity in this patient was 20/40 OD and light perception OS. (Reprinted from Spalton et al.,[4] with permission from Elsevier.)

which the normal posterior pituitary hyperintensity is absent and an ectopic posterior pituitary hyperintensity is seen in place of the necrosed pituitary infundibulum.[1,9] Posterior pituitary ectopia is pathognomonic of anterior pituitary hormonal deficiency with normal posterior pituitary function. The absence of a normal or ectopic posterior pituitary is associated with antidiuretic hormone deficiency. The type of hormonal deficiency may evolve over time in some patients. Growth hormone deficiency is most often associated with optic nerve hypoplasia. Hypothyroidism, hypocortisolism, panhypopituitarism, diabetes insipidus, and hyperprolactinemia may also occur.[11–13] Cerebral hemispheric abnormalities that are often associated with thinning or agenesis of the corpus callosum are predictive of neurodevelopmental defects.[8] Optic nerve hypoplasia with an intact septum pellucidum may be associated with pituitary hormonal deficiencies.[8]

Based on studies with high-resolution neuroimaging, it has been shown that early gestational CNS injury can disrupt optic nerve development.[1,8,14,15] Mass lesions, such as a prenatal suprasellar tumor, may interfere with the normal migration of optic axons to their target sites.[16] Intrauterine injuries to midline CNS structures, such as the septum pellucidum and pituitary infundibulum, can injure or disrupt the migrating axons of the optic nerve.[17] This injury results in direct or transsynaptic retrograde degeneration to cause segmental hypoplasia of both optic nerves.[8,16–18]

Megalopapilla

Megalopapilla refers to an enlarged optic disc with no other morphological abnormalities. In the more common phenotypic variant, megalopapilla more commonly is bilateral. The disc is greater than 2.1 mm in diameter, with an increased cup-to-disc ratio that may mimic normal tension glaucoma.[19] The cupping is usually round or horizontally oval without focal notching of the rim.[20] The axons are spread over a larger surface area causing the neuroretinal rim to appear pale.[21] The less common variant of megalopapilla is unilateral. An anomalous superior excavation obliterates the adjacent neuroretinal rim. This variant is distinguished from a colobomatous disc in which the excavation is located inferiorly on the disc and may be associated with other congenital abnormalities.

In contrast to normal tension glaucoma or compressive optic atrophy, the visual acuity is usually normal or mildly decreased and is often associated with an enlarged blind spot. The differential diagnosis of megalopapilla includes glaucoma, optic disc coloboma, and orbital optic glioma.[22]

Megalopapilla may rarely be seen with other congenital abnormalities, such as basal encephalocele and midline facial anomalies.[23]

Segmental Optic Nerve Hypoplasia

Superior segmental optic nerve hypoplasia may occur in children of insulin-dependent diabetic mothers. These children have no other systemic anomalies and present with incidental inferior visual field defects of segmental optic nerve hypoplasia. Characteristic features include superior entrance of the central retinal artery, superior disc pallor, superior peripapillary halo, and superior peripapillary nerve fiber layer thinning. These funduscopic signs are all suggestive of maternal diabetes.[6,24–26]

Homonymous Hemioptic Hypoplasia

Congenital lesions affecting the retina, optic nerve, chiasm, tract, or retrogeniculate pathways are associated with segmental hypoplasia of the corresponding sections of each optic nerve. Unilateral congenital hemispheric lesions affecting the postchiasmal afferent visual pathways may cause homonymous hemioptic hypoplasia. Transsynaptic degeneration of the optic tract from a retrogeniculate lesion results in homonymous hemioptic hypoplasia, which leads to segmental hypoplasia of the nasal and temporal aspects of the optic disc contralateral to the hemispheric lesion. This optic disc may have horizontal, or "bowtie," pallor. The disc ipsilateral to the hemispheric lesion may be normal to mildly hypoplastic.[14,17,27]

Congenital Tilted Disc Syndrome

The congenital tilted disc syndrome equally affects men and women in 1% to 2% of the population and shows no particular hereditary pattern.[28] It has not been significantly associated with any systemic or neurological disorders. The tilted disc syndrome presents with the following characteristic features: (1) inferonasal "tilting" of the disc with an associated inferonasal crescent (conus), (2) hypoplasia of the retinal pigment epithelium (RPE), and choroid in the inferonasal fundus, (3) posterior staphyloma in the inferonasal region, and (4) situs inversus.[29–31]

The congenital tilted disc syndrome is considered a coloboma that varies in appearance depending upon the degree of malclosure of the embryonic ocular fissure. In the fourth week of gestation, the optic sulci begin to form and grow toward the ectoderm to form the optic vesicles. As the optic vesicle reaches the ectoderm, the distal face invaginates to form a goblet-shaped optic cup that is attached to the forebrain by the optic stalk.[32] This invagination with incomplete closure often results in a coloboma of the optic disc, retina, RPE, and choroids. Because the embryonic ocular fissure closes last in the inferior to inferior nasal aspect, most colobomas arise in this region. The congenital tilted disc syndrome is thought to result from incomplete closure of the ocular fissure at 6 weeks gestation with the formation of a typical coloboma of the disc, peripapillary retina, RPE, and choroids.[29–31,33]

The optic disc only appears to be tilted without actual rotation (Figure 8.3).[4] The superotemporal aspect is elevated and the inferonasal region is posteriorly positioned to form an oval-shaped disc with its long axis obliquely oriented. No actual rotation of the disc occurs in this syndrome. The congenital absence of infero-

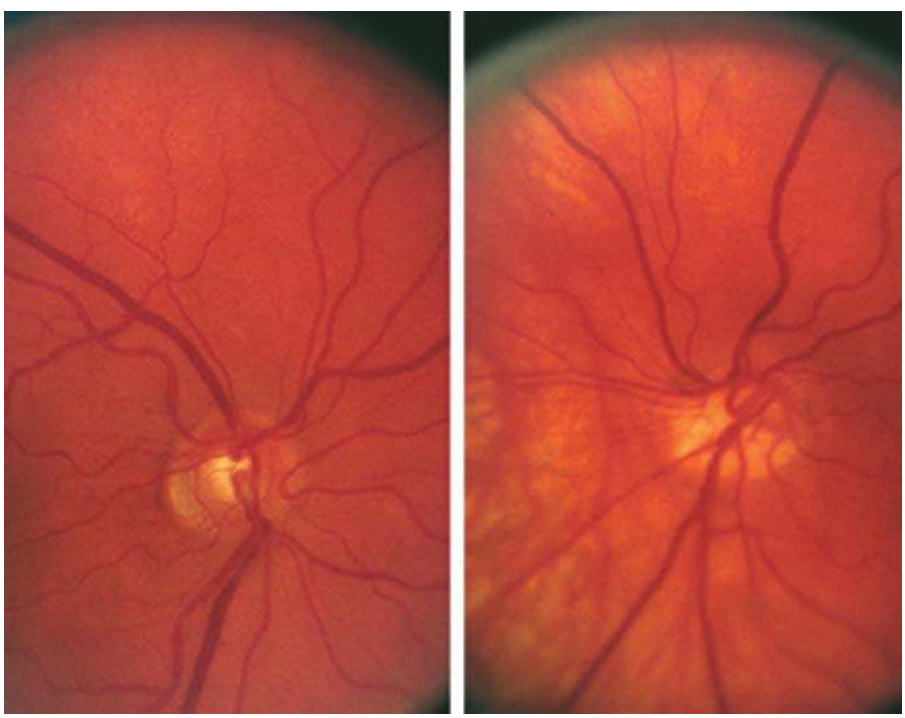

FIGURE 8.3. Congenital tilted disc syndrome. The right optic disc (*left*) is small. The left eye is myopic with a tilted hypoplastic disc (*right*). Myopic retinal pigment epithelial changes can also be seen (*right*). (Reprinted from Spalton et al.,[4] with permission from Elsevier.)

Table 8.1. Clinical features of the congenital tilted disc syndrome

- Congenital tilted disc syndrome is bilateral and nonhereditary.
- Myopia is mild to moderate associated with astigmatism, often with an oblique axis.
- Myopia is nonprogressive, as in acquired high myopia.
- Disc appears tilted inferiorly and nasally.
- Inferior or inferonasal crescent or conus is usually present (Fuch's coloboma).
- Blood vessels emerge from the temporal rather than the nasal aspect of the disc and course nasally before extending outward in the usual temporal distribution (situs inversus).
- Inferonasal fundus appears pale from RPE hypoplasia.
- Posterior, inferonasal staphyloma can be confirmed by computed tomography (CT) scan or B-scan ultrasound.
- Superior temporal or bitemporal visual field defect that does not respect the vertical meridian and corresponds to the area of the inferonasal defect of the optic nerve and retina.
- ERG response is sometimes decreased.

Adapted from Apple et al.[28]

nasal tissue that forms the coloboma gives the appearance that the inferior pole of the disc has been rotated. The superior aspect of the disc appears to be dislocated to the superonasal quadrant. Neural tissue is concentrated at the superior and superior temporal aspect of the disc, whereas the inferior and inferior nasal aspect is deficient in axons. The inferior nasal aspect of the disc is hollowed out and forms an inferonasal conus. The oblique deviation of major retinal vessels toward the inferior crescent contributes to the tilted appearance of the disc. The conus is associated with posterior staphyloma formation and is continuous with an area of hypoplasia of the retina, choroid, and RPE (Table 8.1).[30,31,33]

The region of hypoplasia of the retina, choroid, and RPE is associated with acquired, rare complications, especially choroidal and subretinal neovascularization and hemorrhage.[34–37] The staphylomatous formation is thought to cause stretching of the tissues to form lacquer cracks in Bruch's membrane and a localized nidus for the formation of choroidal neovascularization, which can be treated with parafoveal photocoagulaton. Visual prognosis is relatively good.[37] Associated neovascular membranes that develop in the peripapillary and parafoveal areas do not usually progress.[35] Other less frequently observed findings include associated medullated nerve fibers, central retinal vein thrombosis, and peripapillary and macular subretinal hemorrhages.[34–37]

The appearance of the congenital tilted disc may mimic other acquired ophthalmic syndromes. The lack of nerve fibers in both the disc and inferior peripapillary conus may cause the neuroretinal rim to be nonexistent and may mimic the appearance of notching seen in glaucoma. Furthermore, the inferior conus must be distinguished from the acquired temporal crescent seen in degenerative myopia that enlarges over time.[29,30]

The most common visual field defect seen in the congenital tilted disc syndrome is a superior bitemporal defect not respecting the vertical meridian. It actually represents a refractive scotoma related to the myopia from the inferonasal retina.[31] Larger refractive errors are generally associated with more characteristic presentations of the congenital tilted disc syndrome.[38] The visual field defect may often extend beyond the vertical meridian to form a complete altitudinal defect. Other less common bilateral field defects include arcuate scotomas, blind spot enlargements, and nasal constrictions of the visual field.[38–40]

The most common electrophysiological abnormality observed in the congenital tilted disc syndrome is a delayed latency or no response in the pattern reversal VEP.[41,42] Reduced amplitude of photopic and scotopic b-waves in the electroretinogram (ERG) and reduced amplitude in the electro-oculogram (EOG) reflect defects of the inner retinal layer in the inferonasal area of hypoplasia.[41] The degree of abnormality of the ERG and EOG is proportional to the degree of hypoplasia. The reduced EOG is particularly associated with fundus hypopigmentation.[41]

Ocular and systemic syndromes are associated with the congenital tilted syndrome. The chorioretinal ectasia adjacent with the conus causes the myopic astigmatism with the plus axis oriented parallel to the ectasia.[28] The astigmatic myopia is usually not clinically significant because it is easily correctable and central

vision is not usually affected. In contrast to acquired high myopia, the myopia in congenital tilted disc syndrome is not progressive. The congenital tilted disc syndrome has also been reported to be associated with X-linked congenital stationary night blindness.[28]

Suprasellar disorders have also been associated with the congenital tilted disc syndrome.[43] Suprasellar tumors have been found in patients with the congenital tilted disc syndrome who present with true bitemporal hemianopsia. These tumors may disrupt axons of the optic nerve during migration in embryogenesis.[44] Therefore, an MRI of the brain with contrast is necessary in any patient with the tilted disc syndrome who has a bitemporal hemianopia that resects the vertical meridian.[45]

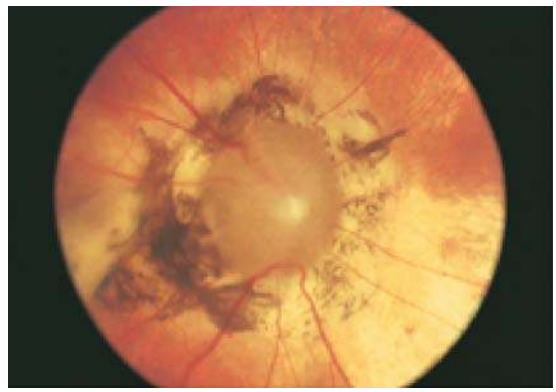

FIGURE 8.4. Morning glory disc anomaly. A mass of glial tissue lies centrally over the disc with radiating retinal vessels. Peripapillary atrophy and pigmentation can be seen. The optic disc lies posterior to the globe within the optic nerve. (Reprinted from Spalton et al.,[4] with permission from Elsevier.)

Excavated Optic Disc Anomalies

Morning Glory Disc Anomaly

The morning glory disc anomaly consists of an optic nerve coloboma associated with retinal vascular anomalies, glial proliferation and metaplasia, and peripapillary pigmentary changes. The embryological origin of this syndrome remains unclear at this time. No hereditary factors have been shown in this condition. The morning glory disc anomaly usually occurs unilaterally in females and rarely in African Americans.[46]

The enlarged optic disc is orange-pink and is located centrally within a funnel-shaped peripapillary excavation. White glial proliferative tissue lies over the center. Chorioretinal pigmentation outlines the disc, and anomalous blood vessels emanate radially from the disc (Figure 8.4).[4] These vessels may be either large and tortuous with S-loops, or abnormally straight, narrow, and branching at sharp angles in the periphery. The macula may occasionally be incorporated into the excavation.[46,47]

Visual acuity is often poor, ranging from 20/200 to finger counting. It is often associated with a myopic astigmatic refractive error.[28] Within the excavated zone, retinal folds and subretinal neovascularization within the surrounding peripapillary pigmentation may be seen. The most common complication of the morning glory disc anomaly is serous retinal detachment, which extends from the peripapillary region to the posterior pole in 26%–38% of patients.[48,49] This complication can lead to transient to permanent visual loss.[48–50] Spontaneous contractile movements attributed to fluctuations in fluid volume between the subretinal and subarachnoid spaces[46] and transient dilation of retinal veins[50] have been reported.

The morning glory disc anomaly can be associated with a transphenoidal encephalocele,[23,51–53] which consists of midfacial deformities, including hypertelorism, depressed nasal bridge, upper lid notch, cleft palate, and herniation of pituitary-hypothalamic structures into an osseous defect in the anterior skull base. The optic chiasm may be absent in one-third of patients, but most have panhypopituitarism.[54] About three-fourths of patients with transphenoidal encephalocele have absence of an optic chiasm, callosal agenesis associated with posterior dilatation of the lateral ventricles.[55] This midline congenital pouch, usually containing the chiasm and adjacent hypothalamus, protrudes through the sphenoid bone and into the nasopharynx to cause rhinorrhea, mouth-breathing, and snoring.[55]

Because hypoplasia of the ipsilateral intracranial vasculature[56] may be associated with the morning glory disc anomaly, magnetic resonance (MR) angiography should be performed. This hypoplasia may occur with or without Moyamoya syndrome.[57]

The morning glory disc anomaly may be associated with ipsilateral orofacial hemangioma as part of the PHACE (*p*osterior fossa malformations, large facial *h*emangioma, *a*rterial anomalies, *c*ardiac anomalies and aortic coarctation; and *e*ye anomalies) syndrome affecting only females.[58]

Optic Disc Coloboma

The optic disc coloboma may occur unilaterally or bilaterally with equal frequency.[59] Unlike the morning glory disc anomaly, there is no predilection for race or sex. The inheritance pattern may be sporadic or autosomal dominant.[59] It has been linked to a mutation of the PAX6 gene. Incomplete or abnormal apposition of the proximal end of the embryonic fissure leads to the development of an optic disc coloboma. The excavation represents the position of the embryonic fissure relative to the primitive epithelial papilla.[59]

An optic disc coloboma appears as a well-demarcated white excavation lying within an enlarged optic disc. This excavation is off centered and lies inferiorly within the disc, distinguishing it from the morning glory disc that lies centrally within the excavation (Figure 8.5).[4] The inferior neuroretinal rim is thin or absent, and the superior neuroretinal rim is relatively spared. In contrast to the morning glory disc anomaly, there is no central glial tuft, no anomalous retinal vasculature, and only minimal peripapillary pigmentary changes. If the defect extends inferiorly to involve the adjacent retina and choroid, then microphthalmia, and iris and ciliary colobomas, may form.[59]

Visual loss is variable and difficult to predict based upon disc appearance. Contractile movements from intrascleral smooth muscle arranged concentrically around the distal optic nerve have also been rarely reported in patients with optic disc colobomas.[60–63] Serous macular detachment can develop in patients with optic disc colobomas; these are nonrhegmatogenous, and spontaneous reattachment has been known to occur.[63,64]

Differing from the morning glory disc anomaly, optic disc colobomas may be associated with other multisystemic congenital syndromes, such as CHARGE,[65,66] Walker–Warburg syndrome,[67] Goltz focal dermal hypoplasia,[67] Aicardi syndrome,[68,69] Goldenhar syndrome,[70] and linear sebaceous nevus syndrome.[67] Orbital cysts may also be rarely seen with optic disc colobomas.[71]

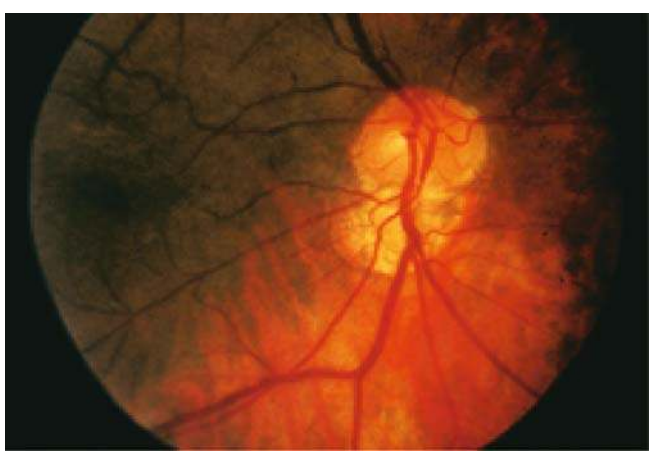

FIGURE 8.5. Optic disc coloboma. The optic disc appears wider horizontally than normal. Inferior to the disc, the coloboma is associated with retinal pigment epithelium hypoplasia. The thinned pigment epithelium inferiorly allows greater visualization of choroidal vessels. (Reprinted from Spalton et al.,[4] with permission from Elsevier.)

Table 8.2. Systemic abnormalities that may be associated with optic disc colobomas

Optic disc colobomas and CNS malformations

- Dandy Walker cyst
- Arhinencephaly
- Anencephaly
- Agenesis of the corpus callosum
- Sphenoidal encephaloceles

Optic disc colobomas and chromosomal abnormalities

- Trisomy 13–15 (Patau's syndrome)
- Trisomy 18 (Edward's syndrome)

Optic disc colobomas and congenital syndromes

- Meckel–Gruber syndrome (autosomal recessive): *coloboma, microphthalmos, cleft palate, micrognathia, polydactyly, renal abnormalities, encephalocoele, and cryptorchidism*
- Goltz syndrome (X-linked dominant): *colobomas, focal dermal hypoplasia, and variable mental retardation*
- Lenz microphthalmia syndrome (X-linked recessive): *colobomas, prominent ears, skeletal defects, and crowded teeth*

CHARGE association: with at least three of the following features:

- Coloboma
- Heart defects
- Atresia of the choanae
- Retarded growth and development
- Genital hypoplasia
- Ear abnormalities and/or hearing loss

Adapted from Jacobs and Taylor.[72]

In the CHARGE syndrome, at least three of the following features must be present for the condition: *c*olobomatous microphthalmia, *h*eart defects, *c*hoanal *a*tresia, *r*etarded growth, *g*enital anomalies, and *e*ar anomalies or deafness (Table 8.2).[72]

Peripapillary Staphyloma

A peripapillary staphyloma appears as a deep, cup-shaped excavation with a relatively normal, well-formed optic disc with some temporal pallor but otherwise normal disc conformation and normal blood vessels. As opposed to the anomalous, poorly defined morning glory disc, the optic disc is located at the bottom of the excavated defect. Unlike the morning glory disc anomaly, central glial tissue and anomalous retinal vasculature are absent. Retinal pigment epithelial and choroidal atrophic changes appear in the walls of the staphyloma. The excavation in the peripapillary staphyloma appears deeper than that of the morning glory disc. Rarely are contractile movement of the walls of the staphyloma observed.[73] Because the optic disc and blood vessels are normally developed, the peripapillary staphyloma formation must occur after the development of these structures. The staphyloma probably occurs during the fifth month of gestation when posterior scleral and neural crest cells are incompletely differentiated. It is believed that normal intraocular pressure may contribute to the herniation of tissue into the weakened scleral wall.[73]

Visual acuity is usually markedly decreased and is associated with a cecocentral scotoma. Peripapillary staphyloma is not usually associated with other congenital anomalies.[73]

Optic Disc Pit

An optic disc pit is a congenital oval or round depression in the optic nerve head. The incidence of optic disc pits is 1 in 11,000,[74] and it usually occurs sporadically. Most optic disc pits occur unilaterally. Optic pits are formed from the herniation of dysplastic retina into a collagen-lined pocket extending posteriorly, often into the subarachnoid space, through a defect in the lamina cribosa.[73] In contrast to optic disc colobomas, optic pits often occur in locations unrelated to the embryonic fissure and are rarely associated with iris or retinochoroidal colobomas or other systemic anomalies.[75]

In unilateral optic pits, the affected disc is slightly larger than the normal one. Optic pits may appear gray, white, or yellowish (Figure 8.6).[4] They average about 0.3 disc-diameters in width and are often located temporally; 20% occur centrally and 10% are located in other regions of the disc.[75] When the pit is located temporally, abnormal peripapillary pigment epithelial changes are often observed. Centrally located pits are associated with temporal disc pallor.[75]

Some common mimics of optic disc pits include glaucoma, central serous choroidopathy, presumed ocular histoplasmosis syndrome, astrocytic hamartoma, melanocytoma, and other types of disc colobomas.[75]

FIGURE 8.6. Optic disc pit. The optic disc pit is located in the temporal (*left*) or inferior aspect of the disc and appears to penetrate deeply. Some patients, as in this example, have serous detachment of the macula and present with visual loss in early adulthood. A late-stage fluorescein angiogram (*right*) reveals hypofluorescence of the pit. (Reprinted from Spalton et al.,[4] with permission from Elsevier.)

Visual acuity is usually normal. Approximately 50% of patients with optic disc pits have visual field defects, which may include a paracentral arcuate scotoma, an enlarged blind spot, a nasal step, a centrocecal scotoma, and generalized constriction.[75]

Temporally located pits are usually associated with serous macular detachment and, occasionally, secondary macular edema and macular hole.[76,77] Larger pits are associated with a higher frequency of serous maculopathy. Macular edema or detachment occurs in about 40% to 60% of patients with optic disc pits. Central visual loss from these macular complications develops at 30 to 40 years of age.[76,77] Spontaneous reattachment is seen in about 25% of cases,[76] but visual recovery has been observed to be variable.[77] The etiology of the intraretinal fluid associated with optic pits remains controversial.

Cilioretinal arteries emerge from or near the optic disc pit in 59% of patients. Approximately 18% of patients have arterial trifurcations.[78]

Papillorenal Syndrome

The papillorenal syndrome consists of bilateral anomalous optic discs associated with hypoplastic kidneys.[79] This disorder has been attributed to mutations in the PAX2 gene, in which several families have been reported with similar eye findings and various renal abnormalities.[80] As the eyes and kidneys are the most highly perfused tissues in the body, lack of angiogenesis in the ocular and renal tissues during development may contribute to this malformation. Failure of the hyaloid system to convert to normal central retinal vessels may lead to optic disc and retinal anomalies.

The excavated disc is not a true coloboma. It has a normal diameter with a central excavation and peripheral pigmentation. Cilioretinal vessels emanate from the disc periphery and the central retinal vessels have variable attenuation.[81] The central retinal circulation is absent. Visual acuity is usually normal and may be decreased by choroidal or retinal hypoplasia or by later complications of retinal detachments. Visual field defects correspond to the regions of retinal hypoplasia.[81]

Optic Disc Dysplasia

Optic disc dysplasia refers to a deformed optic disc that cannot be classified in any specific diagnostic category. It is likely that these optic disc variants will be identified as distinct anomalies in the future.[28]

Elevated Optic Disc Anomalies

Optic Disc Drusen

Optic disc drusen occurs in 3.4 to 24 per 1000 population, and occurs bilaterally in about 75%, and even as high as 91.2%.[82] Although no sex predilection was found in earlier studies, recent investigations note a higher incidence in females of 61%[83] and 71%,[82] respectively. It is inherited as an irregularly autosomal dominant disorder.[84]

The appearance of optic discs having drusen changes with age. In younger children, the drusen is buried within the optic disc, causing disc elevation.[85] In adults, drusen can be seen superficially and the remainder, about 60%, is located deep within the papilla.[86] In a study of six patients,[87] visual field defects can change as fast as within 2.5 years and as slowly as within 9 years.

It is believed that impaired axonal transport through a small scleral canal can lead to axonal degeneration.[88] Based on electron microscopic findings,[89] impaired axonal transport leads to intracellular mitochondrial calcification. Some axons may rupture to release mitochondria in the extracellular space. Calcium continues to deposit in these mitochondria, which gradually degenerate into calcified microbodies to form drusen. Drusen contain calcium,[90] mucopolysaccarides,[91] amino acid,[91] ribonucleic acids,[92,93] deoxyribonucleic acid,[93] and iron.[91]

Most patients with optic disc drusen are asymptomatic. Rarely is visual acuity severely affected by optic disc drusen. Visual loss may follow severe visual field defects.[95] Transient visual obscurations occur in up to 8.6% of cases,[94] and permanent monocular blindness[96] related to optic disc drusen without vascular complications has been documented. When optic disc drusen causes unilateral or asymmetric visual field loss without affecting visual acuity, an afferent papillary defect can be detected on examination.[97] Visual field defects are usually slowly progressive such that patients are not aware of the deterioration of their visual field[98]; sudden defects may rarely occur. Visual field defects increase in extent and frequency beginning in childhood.[99] In a study by Hoover et al.,[99] 18 of 35 eyes in 31 children had an enlarged blind spot, 9 eyes had an inferior arcuate, sector, or altitudinal defect, and 3 eyes had both types of visual field defects. The frequency of visual field defects ranged from 24% to 87%[98,100–102] in adults with superficial drusen and prominent visual field defects. The nerve fiber bundle defects detected by Goldmann perimetry in adults include those in the inferior nasal quadrant, enlargement of the blind spot, and peripheral constriction.[98,100] Most visual loss is in the periphery as a result of arcuate field defects. Blind spot enlargement may be related to concomitant papilledema and vessel leakage.[100]

On funduscopy, drusen may appear buried in the optic disc in children. With increasing age and as calcification progresses with nerve fiber atrophy, the buried drusen become more visible (Figures 8.7, 8.8).[4] In adults, drusen appear as irregular, whitish-yellow crystals within the optic nerve and on the surface of the disc. They are most often in the nasal aspect of the peripapillary area.[102,103] The disc appears elevated with blurred disc margins, but without obscuration of disc vessels or elevation of the peripapillary nerve fiber layer. Drusen occasionally cannot be visually differentiated from intrapapillary refractile bodies in chronic papilledema.[104,105] Disc blood vessels may appear in an anomalous pattern.[103]

Various diagnostic tests are available to help detect and confirm the presence of drusen. Serial automated visual field testing can help determine progression of field defects that correspond to nerve fiber layer damage from the drusen. B-scan ultrasound can detect deeply buried calcified drusen in the optic nerve head, which is seen as bright areas. Deeper lesions can be visualized because of the highly reflective nature of drusen. B-scan ultrasound has been shown to be the most reliable method of detection of drusen.[106] CT scan is not as sensitive as the slice thickness is usually 1.5 mm, which may not detect smaller drusen.[106]

On fluorescein angiography (FA), buried drusen is seen by autofluorescence. The sensitivity of FA is less than that of B-scan ultrasonography.[106] In the late phase of FA, sharply demarcated areas of uneven hyperfluorescence,

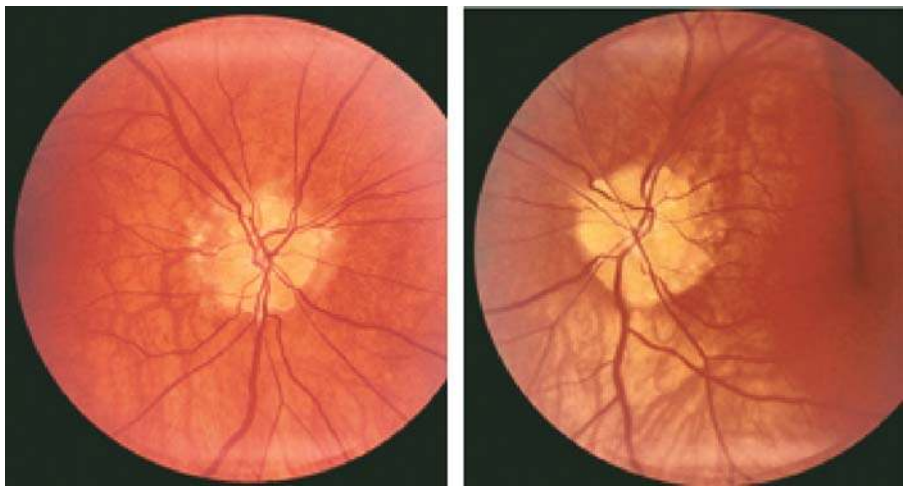

FIGURE 8.7. Optic disc drusen. Drusen appears as crystalline deposits exposed on both discs. The optic discs are relatively small without a cup. The vasculature is anomalous with vessels exiting centrally. The visual fields in this patient were markedly constricted. (Reprinted from Spalton et al.,[4] with permission from Elsevier.)

not usually seen in papilledema, can also be seen.

Optic coherence tomography (OCT) and the GDx scanning laser polarimetry have been used to quantitatively monitor retinal nerve fiber layer loss (RNFL) that could be caused by glaucomatous atrophy obscured by drusen or by optic disc drusen itself. The nerve fiber layer analysis can reveal early subclinical RNFL not visible by fundoscopy. The GDx scanning laser

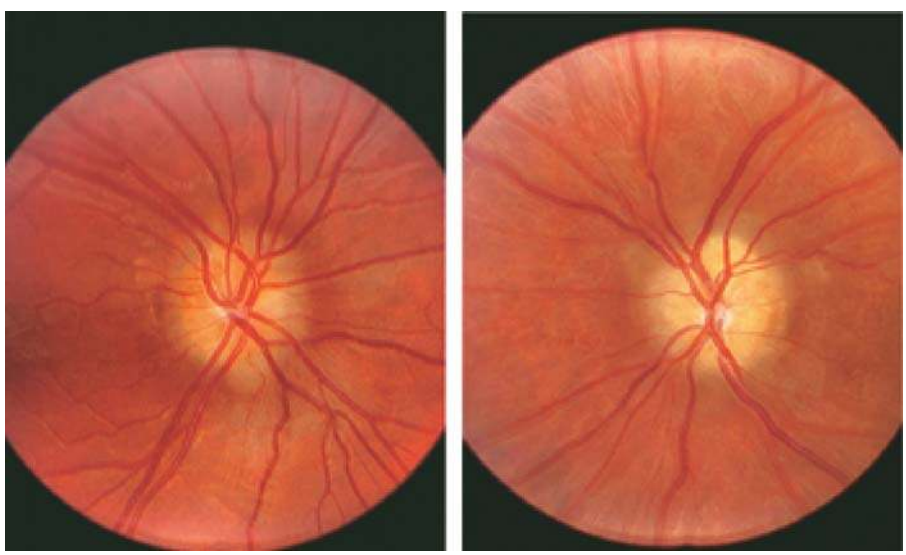

FIGURE 8.8. Subtle disc drusen. Both optic discs have buried drusen that mimic disc swelling. The left disc (*right*) has exposed drusen in the superior aspect. Both discs (*left and right*) are small without a cup. The vessels exit centrally, and the vasculature has anomalous branching. (Reprinted from Spalton et al.,[4] with permission from Elsevier.)

polarimetry has been shown to reliably detect peripapillary thinning associated with optic disc drusen.[107]

VEP is abnormal in 41% to 97% of patients with optic disc drusen[108,109] and represents the severity of peripapillary nerve fiber layer damage.[109] Prolongation of the P100 latency seems to depend on degree of visual impairment and check size used for testing.[108] Earlier VEP components can also be fragmented and of lower amplitude. Because of the wide range of VEP abnormalities seen in patients with optic disc drusen, VEP is not a reliable diagnostic modality for drusen.[109,110]

Sudden, substantial visual field defects can occur as a consequence of vascular complications from anomalies of the ophthalmic arteries and veins that are associated with disc drusen.[111,112] The retinal vessels can be very tortuous and dilated and have abnormal branching with vascular loops.[113] Cilioretinal arteries occur in 20% to 40% of patients with disc drusen[113] compared to 15% in the normal population.[112] Optociliary shunts or venous retinochoroidal collaterals occur in 4% to 6% of patients with disc drusen.[111] Disc drusen account for only 10% of all cases of venous retinochoroidal collaterals.[114] The venous channel between the central retinal and the choroidal circulation may increase with advancing age because of the enlarging drusen that compresses the central retinal vein.[115]

Optic disc drusen is associated with a variety of vascular complications. Nonanterior ischemic optic neuropathy (NAION), occurring in patients with optic disc drusen, is usually related to vaso-occlusion.[116] It affects patients at 20 years of age or less. Optic discs with drusen have smaller diameters than those affected with NAION.[117] The smaller optic nerve canal could lead to more mechanical distortion of blood vessels and would predispose the optic disc to infarction. Enlarging drusen would also cause a compressive ischemia of these vessels.[118]

Central retinal artery occlusion (CRAO) and central retinal vein occlusion (CRVO) also occur in a similar manner as in NAION in patients with disc drusen. Compression of the artery or vein by drusen predispose them to visual loss in the setting of risk factors, such as systemic hypertension, contraceptive use, migraine, high altitude, and atrioseptal defect.[116,118–120]

Subretinal neovascularization in young patients with optic disc drusen is usually located adjacent to the disc and may occasionally extend toward the macula. Visual acuity is usually 6/12 or better after hemorrhage from choroidal neovascular membranes that does not require treatment.[121]

Retinal hemorrhages without subretinal neovascularization usually occur in association with disc drusen. The frequency of retinal hemorrhage is from 2% to 10%.[122] These may be splinter hemorrhages within the nerve fibers, hemorrhages of the optic nerve head spreading to the vitreous, deep papillary hemorrhages, or deep peripapillary hemorrhages with or without extension into the macula. Visual outcome is often good. Visual impairment from macular involvement is rare.[122] The etiology of these hemorrhages is not yet clear. Some possible mechanisms include (1) erosion of the disc blood vessels by enlarging drusen, (2) congestion and venous stasis or retinociliary venous communication, and (3) ischemia.[123]

Optic disc drusen is associated with retinitis pigmentosa and pseudoxanthoma elasticum and angioid streaks. Retinitis pigmentosa occurs up to 39%, based on several series.[124,125] Differing from the idiopathic type, optic disc drusen in retinitis pigmentosa appear adjacent to a normal-diameter disc with a normal scleral canal and a disc that is not elevated.[126]

In pseudoxanthoma elasticum, the incidence of disc drusen ranges from 1.4% to 3.6%.[127] Angioid streaks occur in 85% of patients with pseudoxanthoma elasticum.[127] Disc drusen ranges from 4.5% to 21.6% in some series.[128] These two disorders may have a common genetic biochemical defect of abnormal mineralization that predisposes to the development of disc drusen and angioid streaks. In patients with pseudoxanthoma elasticum, the abnormal accumulation of polyanions with high calcium affinity in the elastic fibers may lead to mineralization of the fibers in the lamina cribosa. Elastin mineralization, as in the angioid streaks, and the deposition of abnormal glycosaminoglycans to elastic fibers of the lamina cribosa

both lead to thickening of the lamina cribosa. The thickened laminar portion of the optic nerve may impair axonal transport. This altered axonal metabolism can predispose to the formation of optic disc drusen despite a normal-sized optic canal.[128]

Treatment for optic disc drusen is often not needed, but monitoring for elevated intraocular pressure and vascular complications as described earlier is recommended. When visual field defects occur, tonometry and visual field examinations should be done regularly. If visual field defects occur with enlargement of optic disc drusen, intraocular pressure-lowering agents should be considered. Optic disc drusen and glaucoma can cause similar types of visual field defects that may be indistinguishable if a patient has both disorders. If the intraocular pressure is elevated in an eye with disc drusen, but without cupping, OCT is recommended to evaluate for RNFL damage.[129] Rarely is surgery ever recommended, but optic nerve sheath decompression was done for visual field loss in 19 eyes, which resulted in significant visual improvement.[130]

Vascular occlusions are treated in a similar manner as in situations without disc drusen. Subretinal neovascular membranes are treated only if central vision is affected. Peripapillary choroidal neovascular membranes related to disc drusen regress spontaneously and do not need photocoagulation. The visual prognosis is relatively good.[122]

Hyaloid System Remnants

The persistence of epipapillary fibrous glial tissue can mimic an elevated optic disc. It can occur unilaterally or bilaterally and may be associated with amblyopia. The vessels in the vitreous during fetal development persist as fibrous glial tissue lying over the disc. The cup may be obliterated, and the disc margins may appear blurred.[28]

The hyaloid vascular system and the glial sheath of Bergmeister, which envelops the posterior portion of the hyaloid artery, have failed to totally atrophy by the end of gestation. The persistence and proliferation of these normally transient vessels of the primary vitreous, especially the posterior tunica vasculosa lentis, leads to the formation of persistent hyperplastic primary vitreous (PHPV) (Figure 8.9).[4] PHPV causes a white pupillary reflex, which must be distinguished from retinoblastoma. Disc anomalies are determined by the extent of persistence of glial and/or vascular components.

A persistent Bergmeister's papilla represents a vascular remnant surrounded by fibroglial tissue or just the fibroglial tissue itself.[131–133] Glial sheath remnants of Bergmeister are epipapillary or peripapillary, off-white membranes or glial cysts.[131–133] These remnants do not impair visual function, but must be distinguished from retinoblastomas, hamartomas of the optic disc, medullated retinal nerve fibers, and papilledema.[28]

FIGURE 8.9. Hyaloid remnants. Glial remnants from either the persistent hyaloid artery or vitreous during embryological development are usually located anterior to blood vessels. The glial tissue can be seen in the inferior aspect of the disc. (Reprinted from Spalton et al.,[4] with permission from Elsevier.)

Anomalous, tortuous vessels and early branching of retinal vessels are commonly seen in patients with persistence of hyaloid remnants. Retinal and ciliary communications, such as cilioretinal, ciliochoroidal, and optociliary vessels, are also seen. Situs inversus, where retinal vessels emerge in a temporal-to-nasal direction, is another associated benign anomaly.[28]

Myelinated Nerve Fibers

Myelination of the optic nerve fibers in the peripapillary retina occurs at a frequency of about 0.3% to 1%.[134] This anomaly is inherited as an autosomal dominant disorder. It affects males and females equally and occurs unilaterally in 80% of patients.[134]

During fetal development at 5 months gestation, myelination progresses from the lateral geniculate body to the optic tracts, then the optic chiasm, and last to the optic nerve by 8 months gestation.[135] Anomalous myelinated nerve fibers develop when myelination extends beyond the posterior portion of the lamina cribosa and into disc and peripapillary areas. The exact pathogenesis of this abnormal extension of myelin is still not well understood.[135]

The myelinated areas have a whitish, feathery appearance and are usually continuous with the disc at the upper or lower poles (Figure 8.10).[4] The myelination may progress after birth but does not usually extend into the macula. Visual acuity is usually normal. More distal myelination into the retina appears fan shaped. If the myelination is more severe, amblyopia, strabismus, nystagmus, enlarged blind spots, and relative scotomas may develop. Myopia occurs in about half of all cases.[134]

Myelinated nerve fibers may be associated with systemic disorders. The Gorlin syndrome (multiple basal cell nevi) is an autosomal dominant disorder that may present in children with myelinated nerve fibers and cutaneous lesions.[136] Typical lesions appear as small pits in the hands and feet that can increase in size and numbers, especially during puberty. Jaw cysts and other bony abnormalities may also develop. Early treatment with dermatological surgery and topical chemotherapy can help prevent progression of this disorder.[137] Myelinated nerve fibers are also associated with an autosomal dominant vitreoretinopathy with limb deformities. The RNFL is myelinated, and the vitreous degenerates to cause congenitally poor vision and night blindness.[138]

Congenital Disc Pigmentation

Congenital optic disc pigmentation is defined as the deposition of melanin anterior to or within the lamina cribosa, giving the disc a slate-gray coloration. This deposition appears irregular and granular.[139] Visual acuity is usually good. Congenital optic disc pigmentation is a rare disorder, but it may be seen associated with Aicardi syndrome[140] and interstitial deletion of chromosome 17.[139]

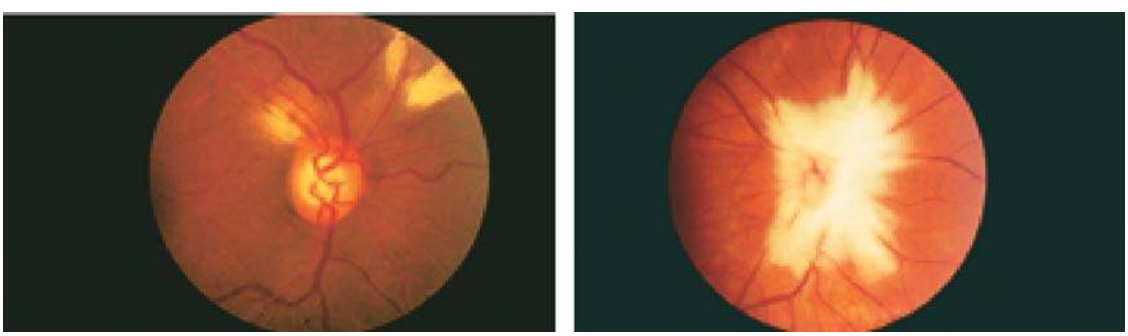

FIGURE 8.10. Myelinated nerve fibers. Myelination of nerve fibers can be seen in the multiple locations in the superior aspects of the fundus on the *left*. Gross myelination over the disc can also be seen on the *right*. (Reprinted from Spalton et al.,[4] with permission from Elsevier.)

Most infants with gray optic discs do not have true congenital disc pigmentation, but rather diffusely gray optic discs related to albinism and delayed visual maturation. This gray tint often disappears within the first year of life without visible pigment migration, and good vision develops. The etiology of this gray tint is unclear. It is thought that the gray color represents delayed myelination of the optic nerve in neonates, but it can also be seen in normal neonates.[141]

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9
Optic Disc Tumors

Jane W. Chan

Tumors of the Sensory Retina and Medullary Epithelium Affecting the Optic Disc

Retinoblastoma

Retinoblastoma affects the sensory retina and is the most common intraocular malignant tumor of childhood that occasionally may extend into the optic nerve. Up to 30% of cases are bilateral. The incidence of retinoblastoma is about 1 in 20,000 live births in the United States.[1] Seventy percent of all retinoblastomas are unilateral and 30% are bilateral. Bilateral cases are transmitted in an autosomal dominant manner with incomplete penetrance.[2] Only 10%–15% of unilateral cases are hereditary.[3] The average age at presentation in bilateral cases is about 10 months and in unilateral cases 21 months.[2]

The most common presentation of a retinoblastoma is leukocoria, followed by strabismus, and then as an ocular disorder that simulates inflammation.[4] Rarely is retinoblastoma manifested as secondary angle-closure glaucoma, proptosis, or pinealoblastoma.[5,6] Some conditions that may mimic a retinoblastoma include (1) persistent hyperplastic primary vitreous, (2) cataract, (3) retinopathy of prematurity, (4) toxocariasis, (5) colobomata of the choroids and disc, (6) uveitis, and (7) Coats' disease.[7]

Retinoblastoma of the optic nerve appears as an elevated, circumscribed gray-white lesion that involves the peripapillary retina. Calcium deposits may be seen within the tumor as it spreads into the overlying vitreous cavity. Feeder vessels from the retina may also enter into the tumor.[1]

About 75% of retinoblastomas demonstrate findings indicative of calcium deposits, which can be detected on computed tomography (CT) scan of the orbits or ultrasound. Magnetic resonance imaging (MRI) of the brain may detect a pinealoblastoma. Ultrasonography may be more helpful in distinguishing retinoblastomas from nonneoplastic conditions.[8,9] DNA analysis on blood specimens from the patient, parents, and any siblings will help confirm the diagnosis. Additionally, a pediatric oncologist should be consulted for a bone marrow aspiration and biopsy, and a lumbar puncture to assess for hematogenous spread of the tumor.

On histopathology the tumor may range from poorly differentiated with mitotic figures to well differentiated with Flexner–Wintersteiner rosettes. These rosettes are composed of columnar cells arranged in a circular manner around a clear central lumen. Retinoblastoma of the optic nerve head may gradually extend into the lamina cribosa and then into the retrolaminar nerve.[2] As it spreads posteriorly along the optic nerve, it may enter the subarachnoid space into the brain. By this time, metastases also occurs in the bone and liver.[10]

If the retinoblastoma remains in the optic nerve anterior to the lamina scleralis, the prognosis is good. If it spreads posterior to the lamina scleralis and into the line of surgical transection of the optic nerve, then the prognosis is worse. Most children who present in the

United States with bilateral retinoblastoma have functional vision in at least one eye after undergoing radiation therapy of both eyes. About 90% of children in the Reese–Ellsworth groups I and II (Table 9.1) and about 30% to 40% of children in group IV and early group V disease have their tumor controlled with good visual preservation. Only 10% to 15% of children with group Vb disease have local tumor control with some retained vision. Thirty percent of eyes treated successfully with radiation therapy have local recurrences, new tumors, or both that require additional treatment with radioactive plaque, cryotherapy, or photocoagulation.[11]

Medulloepithelioma

Medulloepithelioma usually affects the ciliary body and is an exceedingly rare tumor to infiltrate the optic nerve. It is an embryonal tumor arising from the medullary epithelium that eventually develops into the nonpigmented ciliary body epithelium in adulthood.[12] It may develop more posteriorly in the optic nerve.[13]

Table 9.1. The Reese–Ellsworth system of predicting success by external-beam irradiation therapy

Group	Criteria
I	a Solitary tumor less than 4 dd at or behind the equator b Multiple tumors, none larger than 4 dd, all at or behind the equator
II	a Solitary tumor 4–10 dd, at or behind the equator b Multiple tumors, 4–10 dd at or behind the equator
III	a Any lesion anterior to the equator b Solitary tumor larger than 10 dd behind the equator
IV	a Multiple tumors, some larger than 10 dd b Any lesion extending anteriorly to the ora serrata
V	a Massive tumors involving more than half the retina b Vitreous seeding

dd, disc diameter
Adapted from Ellsworth.[11]

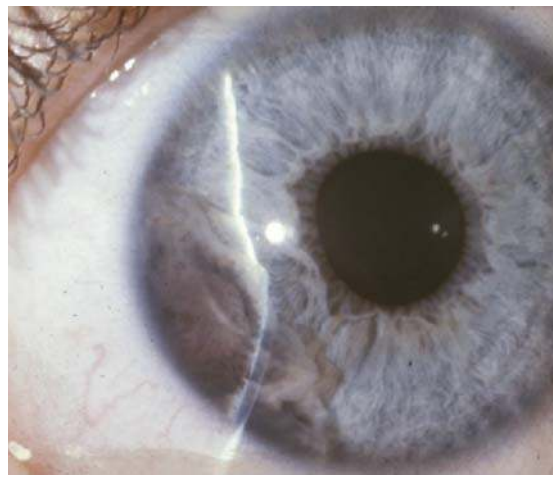

Figure 9.1. Malignant teratoid medulloepithelioma of the ciliary body and iris. This nonpigmented tumor has an irregular surface filling the anterior chamber angle. It may develop posteriorly in the optic nerve, mimicking an astrocytic hamartoma or retinoblastoma. (Reprinted from Atlas of Ophthalmology [http://www.atlasophthalmology.com],[14] with permission from Dr. G. Michelsen.)

It appears as a white-yellow globular mass that may mimic an astrocytic hamartoma or retinoblastoma (Figure 9.1).[13,14] If it extends into the retrobulbar optic nerve, proptosis can occur. Visual prognosis is poor. If the tumor has malignant components, enucleation and removal of the affected optic nerve is the preferred treatment.[13]

Glial Tumors of the Retina Affecting the Optic Disc

Astrocytic Hamartoma of the Optic Disc

Astrocytic hamartomas infiltrate the optic disc to appear to be above the optic disc or in the retina. They occur bilaterally in 50% of patients with tuberous sclerosis complex. The most common type appears as a smooth, flat, salmon-colored lesion that is either round or oval shaped. It is semitransparent and located in the superficial posterior pole of the retina. The second type appears as an opaque, elevated,

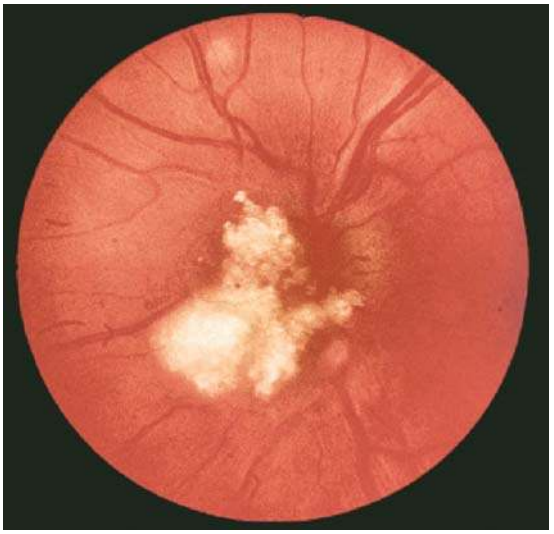

FIGURE 9.2. Astrocytic hamartoma. This white nodular tumor arises from the superficial retina adjacent to the disc and may mimic retinoblastoma or disc drusen. (Reprinted from Spalton et al.,[15] with permission from Elsevier.)

white-yellow calcified tumor with well-defined borders and multiple nodules, resembling a mulberry (Figure 9.2).[15] The third type has a combination of features of the previous two variants. The center is calcified and nodular, while the periphery is smooth, semitranslucent, and salmon colored. The three variants of hamartomas may possibly represent various developmental stages of the tumor.[16,17]

On histopathology, astrocytic hamartomas develop from astrocytes located on the optic nerve head and in the nerve fiber layer of the posterior retina. Astrocytic hamartomas consist of benign astrocytes, calcium, and amorphous material.[18] The lesion is often limited to the prelaminar portion of the disc but may extend through the lamina cribrosa into the retrolaminar portion of the nerve.[19]

On fluorescein angiography, calcified retinal and optic disc astrocytomas may demonstrate autofluorescence. The tumor appears avascular in the early and midphases of the study, and the prominent blood vessels become apparent in the late phases. Diffuse hyperfluorescence occurs because of leakage of dye from these vessels.[20]

Visual function is usually normal unless the optic disc or macula is affected. Diagnosis is based mainly on funduscopic morphological findings, as already discussed. Retinoblastomas of the optic nerve and retina must be differentiated from astrocytic hamartomas. Vitreous hemorrhage may occur rarely, and hard exudates rarely appear surrounding the tumor. Because astrocytic hamartomas usually do not grow and vision is preserved, treatment is not needed.[17]

Astrocytic hamartomas may appear as an isolated phenomenon in 30% of cases.[19,20] The exact prevalence of this tumor is unclear, but astrocytic hamartomas are believed to occur in approximately 53% of patients with tuberous sclerosis complex,[21] and, less commonly, in neurofibromatosis type I (NF-1).[19,22–24]

Tuberous sclerosis complex (TSC) is thought to be transmitted by an autosomal dominant gene with low penetrance and variability of expression.[23] It exhibits locus heterogeneity with two causative loci on chromosome 9p34 (TSC1) and 16p13 (TSC2). The TSC1 gene codes for the protein hamartin, thought to be involved in actin cytoskeleton organization, and the TSC2 gene codes for the protein tuberlin. Both these proteins play a role in GTPase signaling. TSC2 mutations account for about 85% of all cases and appear to cause a more severe disease than TSC1.[25]

Most patients with tuberous sclerosis present with mental retardation, seizures, and adenoma sebaceum, a papular rash in a butterfly distribution over the nose and cheeks.[21] These facial lesions are actually angiofibromas, which are seen in about 75% of patients.[26] In about 25% of patients, shagreen patches, irregularly shaped, raised white "ash leaf" lesions about several centimeters in diameter, can be seen in the lumbar or flank region. Ungual fibromas, nodular lesions adjacent to or underneath nails, are present in 20% of patients.[23]

Besides the retina and the optic disc, astrocytic hamartomas can affect other organs of the body. Calcified hamartomas may be seen in the basal ganglia and ventricles on MRI. Larger tubers may be seen in the cortical gray matter.[23] Hamartomatous lesions can also be found in the heart and are histopathologically classified

TABLE 9.2. Diagnostic criteria for tuberous sclerosis complex: (1) definite tuberous sclerosis complex requires two major features or one major and two minor features; (2) probably tuberous sclerosis complex requires one major feature and one minor feature; (3) possible tuberous sclerosis complex requires either one major feature or two or more minor features

Major features	Minor features
Facial angiofibromas or forehead plaque	Dental pits
Nontraumatic ungula or periungual fibroma	Hamartomatous rectal polyps
More than three hypomelanotic macules	Bone cysts
Shagreen patch	Cerebral white matter migration lines
Multiple retinal nodular hamartomas	Gingival fibromas
Cortical tubers	Nonrenal hamartoma
Subependymal giant cell astrocytoma	Multiple renal cysts
Cardiac rhabdomyoma	"Confetti" skin lesions
Lymphangiomyomatosis	
Renal angiomyolipoma	

Adapted from Roach et al.[27]

as rhabdomyomas. In the kidney, they appear as angiomyolipomas and are present in about 80% of patients with tuberous sclerosis.[23]

Diagnosis is based on clinical criteria (Table 9.2) and can be confirmed with molecular gene testing for chromosome 9q34 and chromosome 16p13.[27]

Treatment for astrocytic hamartomas is not usually necessary as they are benign, stable lesions that often do not affect visual acuity. About 80% of patients with tuberous sclerosis complex have epilepsy, mental retardation, developmental delay, and autism.[27] This neurological involvement is often the most common cause of morbidity in tuberous sclerosis complex patients. Therefore, a patient who presents with an isolated astrocytic hamartoma in the fundus needs a neurological examination and an MRI of the brain as part of the evaluation for tuberous sclerosis complex. Because astrocytic astrocytomas can also be rarely seen in NF-1, the neurological evaluation should also be focused on detecting this disorder.[27]

Vascular Tumors of the Retina Affecting the Optic Disc

Capillary Hemangioma

Capillary hemangiomas are bilateral in one-third to one-half of affected persons between the ages of 15 and 40. Capillary hemangiomas may present as an endophytic lesion that looks circular, reddish-orange, elevated, and well circumscribed involving a portion of the disc or the entire disc and juxtapapillary retina (Figure 9.3).[14] It lies underneath the internal limiting membrane and grows inward toward the vitreous cavity. It may also mimic a peripapillary subretinal neovascular membrane. The exophytic type of capillary hemangioma appears as an indistinct lesion, causing a blurred and elevated disc margin, often with serous detachment, or the peripapillary sensory retina and a ring of lipid deposition. Although capillary hemangiomas of the optic disc may mimic optic disc granulomas, optic neuritis, peripapillary

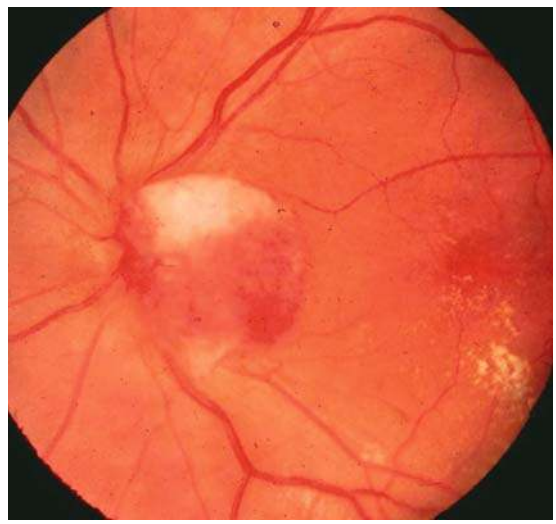

FIGURE 9.3. Capillary hemangioma of the disc in von Hippel–Lindau syndrome. This pink, well-defined tumor over the disc is surrounded by mild hemorrhage and chronic macular exudates. (Reprinted from Atlas of Ophthalmology [http://www.atlasophthalmology.com],[14] with permission from Dr. G. Michelsen.)

subretinal neovascularization, or even papilledema if presenting bilaterally, fluorescein angiography or ultrasound can demonstrate the vascular anomaly. The capillaries of the tumor fill in the retinal arterial phase of the angiogram, and the tumor becomes hyperfluorescent from leakage of fluorescein dye. These tumors in the optic disc do not demonstrate large feeding and draining vessels as do those in the peripheral retina.[28]

On histopathology, capillary hemangiomas of the optic disc consist of a proliferation of capillaries in the disc and vacuolated interstitial cells.[29] These capillaries may extend into the juxtapapillary retina, which may have cystic changes in the outer plexiform layer.[30]

On B-scan ultrasonography, the capillary hemangioma appears as a mass lesion with a smooth anterior border, acoustic solidity, and no choroidal exacavation. A-scan ultrasonography reveals an initial high spike with low or medium internal reflectivity.[31]

The most common presenting symptom, painless visual loss, occurs in 53% of cases.[32] This visual loss is often a result of associated subretinal and intraretinal fluid and hard exudates. Blindness can occur if the tumor grows and a large nonrhegmatogenous retinal detachment evolves. Vitreous hemorrhage and neovascular glaucoma are rare.[32,33] About one-third of affected patients have more than one lesion, which is often present at different stages of maturation. About 50% of patients with a capillary hemangioma of the optic disc also have an associated retinal capillary hemangioma in the involved eye.[34] These vascular tumors do not extend into the optic nerve or chiasm.

About 25% of patients with a capillary hemangioma of the optic disc and/or retina have an associated central nervous system (CNS) hemangioma. Capillary hemangiomas may be a feature of a rare disorder, von Hippel–Lindau disease (see following section: Optic Disc Hemangioblastoma). Other systemic abnormalities that can be associated with capillary hemangiomas include pheochromocytoma and renal cell carcinoma.[35] Angiomas and cysts of the pancreas, liver, spleen, kidney, lung, ovaries, epididymis, and bladder have been reported to be associated with this ocular vascular anomaly.[32,36]

Definitive criteria for treatment of capillary hemangiomas of the optic disc have not been established at this time. Small retinal capillary hemangiomas, less than about 2.5 mm disc diameters, that are not associated with the optic nerve can be treated with direct argon laser photocoagulation.[37] Cryotherapy[38] or perforating diathermy with or without scleral buckling[39] is reserved for larger lesions. These types of therapy are not applied to tumors of the optic disc because of the risk of permanent visual loss. Photocoagulation over the surface of the tumor has been done in patients with visual loss from macular edema or macular subretinal fluid. Only about a third of these patients maintained pretreatment vision after photocoagulation.[40]

Cavernous Hemangioma

Cavernous hemangioma of the optic disc consists of grapelike clusters of aneurysmal dilatations of large-caliber vessels located within and above the optic disc (Figure 9.4).[14] The tumor may cover a portion or all of the optic nerve head and may even extend into the peripapillary retina. It usually occurs unilaterally and

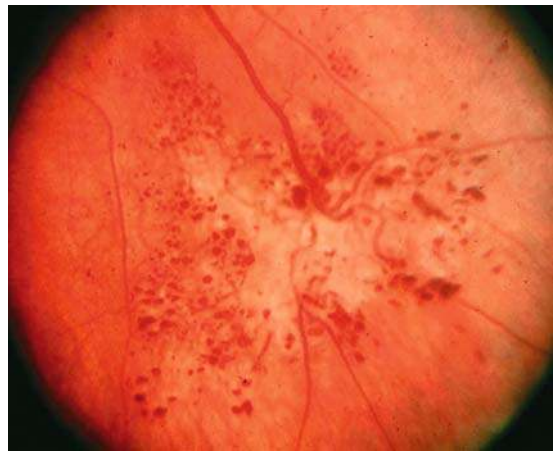

FIGURE 9.4. Cavernous hemangioma of the retina. This cluster of small aneurysms, which are filled with stagnant blood, is located over the disc. (Reprinted from Atlas of Ophthalmology [http://www.atlasophthalmology.com],[14] with permission from Dr. G. Michelsen.)

may be inherited in an irregular autosomal dominant pattern. According to a study by Lewis et al.,[41] the average age of presentation was 23 years and 60% of these tumors occurred in women. Less than 10% were bilateral. Visual acuity is usually spared, unless the fovea is involved. Visual fields often reveal an enlarged blind spot. Progression of these lesions is rare, and vitreal hemorrhage is unusual. In contrast to capillary hemangiomas of the optic disc and retina, yellow intraretinal and subretinal exudation is not associated with cavernous hemangioma.[41]

On histopathology, cavernous hemangiomas consist of large vascular spaces lined with epithelial cells. These spaces replace the normal nerve tissue but do not extend posterior to the lamina cribosa. These tumors extend through the full thickness of the peripapillary retina, but not to the choroid.[42]

On fluorescein angiography, the flow through a cavernous hemangioma is slower and is often hypofluorescent in the early stages. The tumor may not entirely fill until the venous phase or later. Some saccules fill completely, whereas others demonstrate an upper portion of dye and a lower portion of erythrocyte plasma. Some tumors may remain hypofluorescent even in the late stages. Slight staining may be seen, but extravascular leakage from the tumor is not commonly seen.[41]

On B-scan ultrasonography, the cavernous hemangioma appears as an elevated dome-shaped mass with an anechoic area inside, and no choroidal excavation. A-scan ultrasonography reveals a high initial spike and irregular reflectivity.[31]

In contrast to capillary hemangiomas, cavernous hemangiomas may grow within the retrolaminar, intracanalicular, and intracranial optic nerve, optic chiasm,[43,44] or optic tracts to cause a gradual compressive optic neuropathy with subsequent visual loss. More commonly, sudden hemorrhage of the cavernous hemangioma may cause sudden headache, acute decrease in visual acuity, and visual field defects. Up to one-third of patients may present with transient visual loss. Cavernous hemangiomas localized only to the optic disc may grow in size and even cause vitreous hemorrhage severe enough to require vitrectomy.[45] Alcohol abuse, pregnancy-related hormonal changes, and Valsalva maneuver have been associated with a higher risk of aneurysmal rupture, especially in patients between 30 and 40 years of age.[44,45]

In contrast to capillary hemangiomas, cavernous hemangiomas are not associated with von Hippel–Lindau disease, but they are associated with systemic abnormalities, including various cavernous hemangiomas of the skin and brain. The intracranial hemangiomas may cause seizures and intracranial hemorrhage.[44,45]

Treatment is not necessary in most cases because cavernous hemangiomas grow slowly and rarely cause spontaneous vitreous hemorrhage. Cryopexy and photocoagulation might be useful in preventing further vitreous hemorrhage from retinal cavernous hemangiomas,[46] but this therapy for optic disc variants is not established at this time.

Optic Nerve Hemangioblastoma

In contrast to capillary and cavernous hemangiomas, optic nerve hemangioblastomas are malignant.[47] Optic nerve hemangioblastomas grow within the nerve parenchyma to cause an anterior or retrobulbar optic neuropathy, which may be either unilateral or bilateral (Figure 9.5).[14,47,48,49] Optic nerve hemangioblastomas contain a vascular matrix with intervascular stomal cells with abundant cytoplasm. These vascular spaces are lined with endothelium, pericytes; lipid-filled stromal cells fill the intervascular areas.[48]

Patients present with progressive visual acuity loss, a relative afferent pupillary defect, and variable visual field defects. On MRI, the affected optic nerve appears enlarged and fusiform, mimicking an optic nerve glioma.[50]

Thirty percent of optic disc hemangioblastomas are associated with von Hippel–Lindau disease.[47] The prevalence of von Hippel–Lindau disease has been found to be 1 in 10,000 to 1 in 22,000.[51] This disorder consists of retinal and/or optic disc hemangioma and CNS hemangioblastoma, most commonly occurring in the cerebellum and less often in the medulla and spinal cord.[35,36] The average age of onset of this

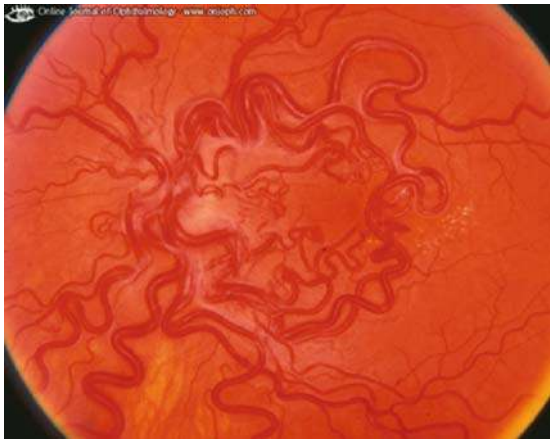

FIGURE 9.5. Optic nerve hemangioblastoma of Wyburn-Mason syndrome. This malignant vascular "bag of worms" grows within the nerve parenchyma to cause an anterior or retrobulbar optic neuropathy. (Reprinted from Atlas of Ophthalmology [http://www.atlasophthalmology.com],[14] with permission from Dr. G. Michelsen.)

disorder is 32 years, but retinal vascular lesions may occur at a younger age (10 years and older) to cause visual impairment from hemorrhage.[52] Up to half of cases of von Hippel–Lindau disease are autosomal dominant with variable penetrance.[51] The remainder of cases are probably sporadic.[34] The gene for von Hippel–Lindau disease is a tumor suppressor gene that maps to chromosome 3p25. Genetic testing can help refine diagnostic criteria (Table 9.3). Ophthalmoscopy, renal ultrasound, and MRI of the brain with contrast should be done every 3 years.[53]

TABLE 9.3. Clinical diagnostic criteria for von Hippel–Lindau disease

Without family history of von Hippel–Lindau	With family history of von Hippel–Lindau
Two or more hemangioblastomas	Single hemangioblastoma
OR	OR
Single hemangioblastoma	Two of the following:
AND	Renal cell carcinoma
One of the following:	Pheochromocytoma
Multifocal renal cyst	
Renal cell carcinoma	
Pheochromocytoma	

Adapted from Rosenberg et al.[53]

Visual loss secondary to optic nerve hemangioblastomas may be preventable with surgical treatment.[47,54] Resection of the hemangioblastoma with preservation of the optic nerve is possible because the pattern of growth produces a plane of section between the tumor and the optic nerve.[47] If the lesion grows circumferentially around the nerve, then resection may involve permanent damage to the optic nerve. In a report by Aiello et al.,[55] 4 weeks of systemic therapy with vascular endothelial growth factor (VEGF) receptor inhibitor SU5416 in a patient with von Hippel–Lindau syndrome and optic nerve head hemangioblastoma experienced improved visual function that was maintained over 18 months with intermittent SU5416 therapy. Visual acuity improved from 20/32 (–2) to 20/16 (–1), the visual field expanded from a circumferential constriction within 8° of fixation to normal, and contrast sensitivity improved in all except the lowest spatial frequency (1.5 cycles/degree). The size of the hemangioblastoma did not change by fundus photographic measurements.

Racemose Hemangioma

Racemose hemangiomas are rare arteriovenous anastomoses, consisting of an engorged retinal vessel that enters the optic disc, then into the peripheral retina, and finally out of the optic disc (see Figure 9.5).[14] These hemangiomas usually occur unilaterally and are thought to be congenital abnormalities, but remodeling may occur over years.[56] On histopathology, racemose hemangiomas have a variable fibromuscular medial layer that makes it difficult to distinguish the vessels as either arterial or venous. These vessels may compress the optic nerve and replace normal tissue in the nerve and even the full thickness of the retina.[57]

About one-third of racemose hemangiomas are associated with the Wyburn-Mason syndrome, involving arteriovenous malformations in the midbrain that are ipsilateral to a separate retinal lesion. Rarely, an intracranial arteriovenous malformation may extend anteriorly

through the optic foramen, along the optic nerve to the retina, all as one lesion.[58] Growth into the orbit and orbital portion of the optic nerve can cause diplopia, proptosis that is usually nonpulsatile, an orbital bruit, and conjunctival vascular dilatation.[59,60] Intracranial and retinal arteriovenous malformations are also associated with vascular malformations in the ipsilateral maxilla, pterygoid fossa, and mandible to cause epistaxis.[61] They can be located in the ipsilateral frontal areas to cause seizures, intracranial hemorrhage, hemiplegia, and homonymous visual field defects. They can also affect the posterior fossa to cause cranial nerve palsies and other brainstem signs.[62–64]

Visual acuity is preserved when a racemose hemangioma has small arteriole–venule anastomoses that involve one sector of the retina and are difficult to detect on funduscopy. However, vision is often impaired when retinal veins grow tortuous and irregularly dilated, mimicking aneurysms. Occasionally several large vessels may grow to obscure the disc to impair vision. The most severe type involves markedly convoluted, dilated, and tortuous arteriovenous communications that drain the macula both superiorly and inferiorly to the horizontal raphe. Central retinal vein occlusion may be a complication, leading to neovascular glaucoma.[23,56,65] The enlarged veins, giving the appearance of a bulky lesion, can develop thrombosis or may directly compress the central retinal vein.[66] If an associated intracranial hemangioma affects the optic tract, then a homonymous hemianopsia is seen.[65]

On fluorescein angiography no leakage occurs in the racemose hemangioma, so flow is rapid. The vascular malformation may appear as small, abnormal vessel communications or as an extensive, tortuous "bag of worms."[2]

The workup of an isolated racemose hemangioma in the retina includes a neurological evaluation and neuroimaging, such as an MRI of the brain, to identify an intracranial arteriovenous malformation. If the neurological exam is abnormal, then cerebral angiography may also be considered. Visual prognosis of racemose hemangiomas depends on the location and size of the lesions. They are usually stable and often do not require treatment. Periodic ophthalmologic and neurological examinations should be performed to monitor this disorder.[2]

Melanocytic Tumors Affecting the Optic Disc

Melanocytoma

Melanocytoma of the optic nerve usually presents unilaterally as a congenital pigmented nevus that appears dark brown or black (Figure 9.6).[15,67] It is a relatively benign tumor of the optic disc that is often diagnosed at about 50 years of age and does not appear to have a racial predilection.[68] This tumor is not associated with systemic disorders, but it is associated with an 8% incidence of ocular melanocytosis.[68]

On histopathology, melanocytomas are composed mainly of two types of cells. The type 1 cell is oval or round, containing giant, round cytoplasmic melanosomes. Nuclei and nucleoli are small. The type 2 nevus cell is spindle shaped, with larger nucleoli, rod-shaped melanosomes, and more cytoplasmic organelles.[69,70]

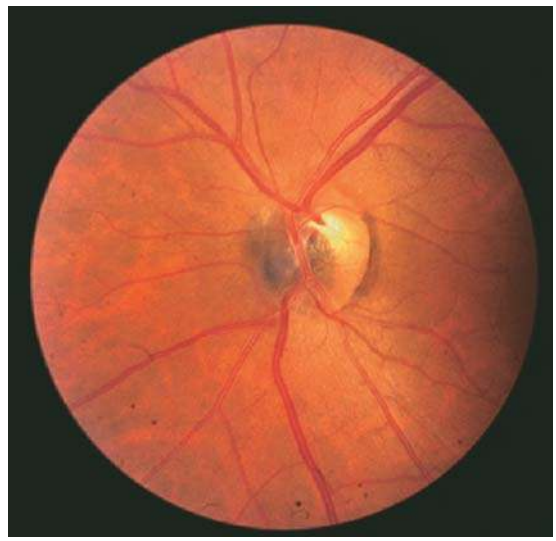

FIGURE 9.6. Melanocytoma. This pigmented benign tumor is often located in the inferior aspect of the disc. (Reprinted from Spalton et al.,[15] with permission from Elsevier.)

Some conditions to consider in the differential diagnosis of an optic disc melanocytoma include juxtapapillary choroidal melanoma, choroidal nevus, hyperplasia of the retinal pigment epithelium (RPE), combined hamartoma of the retina and RPE, adenoma of the RPE, metastatic melanoma to the optic disc, and epipapillary vitreous hemorrhage.[68]

Seventy-five percent of patients with melanocytoma have visual acuity ranging from 20/15 to 20/30.[67] Mild visual loss is attributed to the tumor from retinal exudation involving the fovea or neuroretinitis from tumor necrosis.[67] Severe visual loss occurs rarely and is often a result of central retinal vein occlusion and/or spontaneous tumor necrosis.[71–76]

An afferent pupillary defect occurs in about 30% of patients with optic disc melanocytomas in the affected eye.[77] Mild compression of the optic nerve fibers by melanocytoma cells may lead to this pupillary defect in the setting of good visual acuity.

Visual field defects occur in most patients with optic disc melanocytomas. An enlarged blind spot occurs in 75% of affected patients, arcuate scotomas in 20%, a nasal step in 10%, relative nerve fiber bundle defect in 20%, and an absolute arcuate defect in 20%.[77] Tumor extension beyond the disc margin may cause an enlarged blind spot. Nerve fiber layer field defects may be related to tumor compression of the axons in the optic disc.

An optic disc melanocytoma appear as a dark brown to black, elevated mass that grows within the substance of the optic disc. Approximately 90% of melanocytomas measure two disc diameters or less, and most are 1 mm in height.[67] Eleven percent of these melanocytomas increase in size by 5 years and 32% of them by 10 years.[73] Fifteen percent are confined to the optic disc, and the remainder may be located eccentrically on the disc to affect the nerve fiber layer of the peripapillary retina, giving the appearance of a feathery margin. In 54% of affected patients, this tumor extends beyond the disc margin to involve the adjacent choroid. In 30% of affected patients, it grows into the adjacent sensory retina.[78]

Fluorescein angiography often reveals persistent hypofluorescence throughout the study. This finding is related to the densely packed, deeply pigmented cells and avascularity of the tumor. If optic disc edema is present, then hyperfluorescence of the disc can be seen adjacent to the tumor.[79,80] B-scan ultrasound or CT scan detect this tumor if it is elevated beyond the disc more than 0.5 mm. Optical coherence tomography (OCT) can detect subretinal fluid and cystoid macular edema.[81]

Optic disc melanocytomas display a variety of local complications that account for visual loss in about 26% of affected patients. In a study of 115 patients with melanocytoma of the optic disc,[73] optic disc edema was seen in 25%, retinal edema in 16%, localized subretinal fluid in 14%, retinal exudation in 12%, retinal hemorrhage in 5%, vitreous seeds in 4%, and retinal vein obstruction in 3%. Optic disc edema adjacent to the tumor is seen more often in larger tumors. This edema is thought to represent axoplasmic stasis from chronic disc compression.

About 54% of optic disc melanocytomas had a choroidal component and 30% had a retinal component. Mild peripapillary subretinal fluid is seen in 10%, and vascular sheathing may be seen in one-third of cases. The spread of the tumor to the retina and the development of subretinal fluid appear to be risk factors for visual loss that is usually not severe.[73]

Severe visual loss, however, may be caused by tumor necrosis and retinal vascular occlusion. Rarely, patients may develop spontaneous necrosis of the tumor and surrounding neural tissue from chronic compression of disc vessels. This necrosis can induce obstruction of the central retinal vein and retinal hemorrhages.[81] The visual outcome is poor.

Although melanocytomas are considered to be benign lesions that do not usually require any treatment, they have the potential to produce the aforementioned ocular complications.[81] Tumor growth may lead to ischemic tumor necrosis and visual loss and not be associated with malignant transformation. Therefore, affected patients should have fundus photos with their eye examination every year.[81] Clinical features suggestive of malignancy at presentation include moderate visual loss, marked elevation, and atypical B-scan echogra-

phy are indications of possible malignant change de novo or from the juxtapapillary choroids.[82] If progressive growth of the tumor occurs with worsening visual loss, then enucleation should be considered.[81]

Choroidal Melanoma

The most common symptoms in patients with a choroidal melanoma are visual loss, photopsias, and visual field defects. Some are asymptomatic. Visual loss is usually a result of the tumor extending to the disc or fovea, exudative retinal detachment involving the macula, or tumor encroaching on the lens. Choroidal melanomas have a racial predilection for Caucasians that is eight times that of blacks[83,84] and three times that of Asians.[85,86]

Because a choroidal melanoma may have various atypical features, it can mimic other lesions, such as a choroidal nevus, a localized retinal hemorrhage, an RPE tumor, or a choroidal hemangioma. A melanocytoma of the optic disc may mimic a combined hamartoma of the retina and retinal pigment epithelium, which has tortuous blood vessels and macular pucker, or an optic disc pit, which appears as an excavated lesion. In contrast to an optic disc melanocytoma, a peripapillary melanoma is not deep black and often grows over a period of months. Melanomas also do not have a feathery margin.[87]

Although the classic choroidal melanoma presents as a pigmented, dome-shaped tumor with an associated exudative retinal detachment, it is the less common presentations of a choroidal melanoma that encroach onto the optic disc. Most optic disc melanomas arise from direct extension of juxtapapillary choroidal melanomas (Figure 9.7).[14] Infiltration of the optic disc and subarachnoid space is more likely to occur from diffuse choroidal melanomas than from nodular ones. They appear as juxtapapillary, subretinal, brown or yellow lesions with variable surface pigmentation. Diffuse melanomas are flat, usually less than 5 mm thick, and cover more than 25% of the uveal tract.[88] Gradual infiltration of the disc may cause worsening optic disc edema and central retinal vein obstruction.[89]

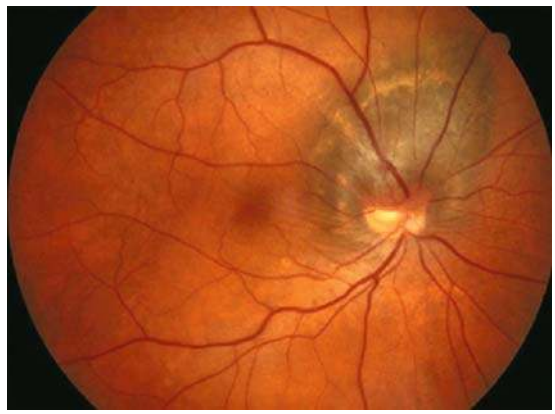

FIGURE 9.7. Juxtapapillary choroidal melanoma. Most optic disc melanomas arise from direct extension of juxtapapillary choroidal melanomas. This dark elevated tumor involves the upper aspect of the optic disc. Infiltration of the optic disc is more likely to occur from diffuse, rather than nodular, choroidal melanomas. (Reprinted from Atlas of Ophthalmology [http://www.atlasophthalmology.com],[14] with permission from Dr. G. Michelsen.)

On fluorescein angiography, diffuse choroidal melanomas affecting the optic disc appear as diffuse hyperfluorescence or as hyperfluorescence mottled with areas of hypofluorescence. Lesions that appear hyperemic on fundoscopy have uniform hyperfluorescence of the disc on angiography. These clinical findings correlate with tumor impinging upon the disc at the level of the lamina choroidalis without invasion of the optic nerve head. This compressive effect from the tumor may contribute to the disc edema. White tissue on the surface of the disc appears hypofluorescent in the earlier phases of the angiogram and correlates histopathologically with tumor tissue that may have infiltrated the optic nerve itself.[89]

Tumor that has infiltrated the disc of a patient with poor vision is best managed by enucleation with a long resection of the optic nerve. Optic nerve invasion is correlated with development of metastases.[90] Radiotherapy, thermotherapy, and other techniques are more effective for local tumor control.[91]

Combined Hamartoma of the Retina and Retinal Pigment Epithelium

The combined hamartoma of the retina and RPE is a benign, congenital hamartoma involving the pigment epithelium, sensory retina, retinal vasculature, and adjacent vitreous. It affects males and females equally and is usually diagnosed about 15 years of age.[92]

On histopathology, the combined hamartoma of the retina and retinal pigment epithelium on the disc is composed of glial, vascular, and pigmented cells that replace the normal tissues of the retina and optic nerve. Infiltration of the hyperplastic RPE into the retinal layers and along the inner retinal surface is seen. Glial and fibrous tissue gives a gray-white appearance to the center of the lesion. This gliosis accounts for the vascular tortuosity, tractional folding of the retina, and vitreoretinal interface changes.[92,93]

Visual loss is unilateral and painless. Visual acuity ranges from 20/40 to 20/200.[93–95] Visual loss occurs more commonly in patients who have lesions involving the optic disc caused by contraction of surface glial tissue that leads to striae distorting the fovea.[95] In a study by Schachat et al.,[95] 18% of the tumors were located on the optic disc, 28% were in the juxtapapillary area, 38% involved the macula, 10% involved both optic disc and fovea, and only 5% were in the midperiphery. Other features can include hyperpigmentation, tortuosity of vessels, mild elevation, and occasionally an epiretinal membrane. Contraction of the inner aspects of the tumor causes surrounding vessels and retina to be drawn toward its center. These tumors usually do not grow, but growth has been reported in a few patients.[93,96] The contraction of the glial tissue can decrease vision and give the appearance of tumor growth.[96]

On fluorescein angiography, the early venous filling phase shows tortuous vessels and dilated retinal capillaries. These abnormal vessels show leakage in the later phases of the study. Ultrasound may be useful in ruling out other disc tumors, because combined hamartoma of the retina and RPE is only minimally elevated and is not well seen on ultrasonography. Complications of combined hamartomas of the retina and RPE include choroidal neovascularization, progressive retinoschisis, retinal hemorrhages, vitreous hemorrhages, exudative retinal detachment, and subretinal and intraretinal exudation.[97–99]

It is important to distinguish combined hamartoma of the retina and RPE from retinoblastoma. Choroidal nevi, melanomas, reactive hyperplasia of the retinal pigment epithelium, and melanocytoma may all mimic combined hamartomas of the retina and retinal pigment epithelium. Gliosis and traction are often absent in nevi, melanomas, and melanocytomas. Reactive hyperplasia of the pigment epithelium appears more irregular than in combined hamartoma.[92,99]

Although the combined hamartoma of the retina and retinal pigment epithelium usually occurs in individuals with no underlying systemic abnormalities, several reports have shown that they may be one of the ophthalmic manifestations of the phakomatoses, especially neurofibromatosis types I and II.[100–103] Juvenile nasopharyngeal angiofibroma has also been associated with combined hamartoma of the retina and retinal pigment epithelium.[104]

Some reports have shown visual improvement in patients with combined hamartoma of the retina and RPE after pars plana vitrectomy and membrane peeling for vitreoretinal traction.[105–107] Subfoveal choroidal neovascularization associated with combined hamartoma of the retina and retinal pigment epithelium can be treated successfully by submacular surgery.[108] Based on the results from a study of 41 patients over 4 years by Schachat et al.,[95] 66% of patients remained within 2 lines of their initial visual acuity, 24% decreased greater than or equal to 2 lines, and 10% improved by greater than or equal to 2 lines. Three patients underwent patching, and one had vitreous surgery with membrane peeling. However, vitrectomy done on 2 other patients in this study did not improve vision. It is suggested that when peeling the macular epiretinal membrane, it is difficult to separate it from the tumor, and some of the retinal tractional folds remain after surgery.[109]

Metastatic Tumors

Systemic Cancers, Leukemia

See Chapter 4: Compressive and Infiltrative Optic Neuropathies.

Intrinsic Optic Nerve Tumors

Benign and Malignant Gliomas, Optic Nerve Sheath Meningiomas

See Chapter 4: Compressive and Infiltrative Optic Neuropathies.

Other Granulomatous Lesions

Sarcoidosis

See Chapter 4: Compressive and Infiltrative Optic Neuropathies.

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10
Optical Coherence Tomography in Optic Nerve Disorders

Julio A. Rodríguez-Padilla and Thomas R. Hedges III

Introduction

Optical coherence tomography (OCT) is an evolving technology that provides noninvasive imaging of tissues. It uses low coherence interferometry to produce cross-sectional images based on the optical scattering of light,[1] similar to ultrasound. Since its introduction into the ophthalmology clinic in the 1990s, optical coherence tomography has become a standard tool for the evaluation of ophthalmic disease. Although its main use was initially for retinal disease and glaucoma, OCT now has a niche in neuro-ophthalmic evaluation. It is mainly useful to rule in occult retinal disease when the etiology of visual loss is unclear, but it is also used to evaluate and follow up abnormalities of the retinal nerve fiber layer (RNFL), such as optic nerve edema and atrophy.[2]

Techniques

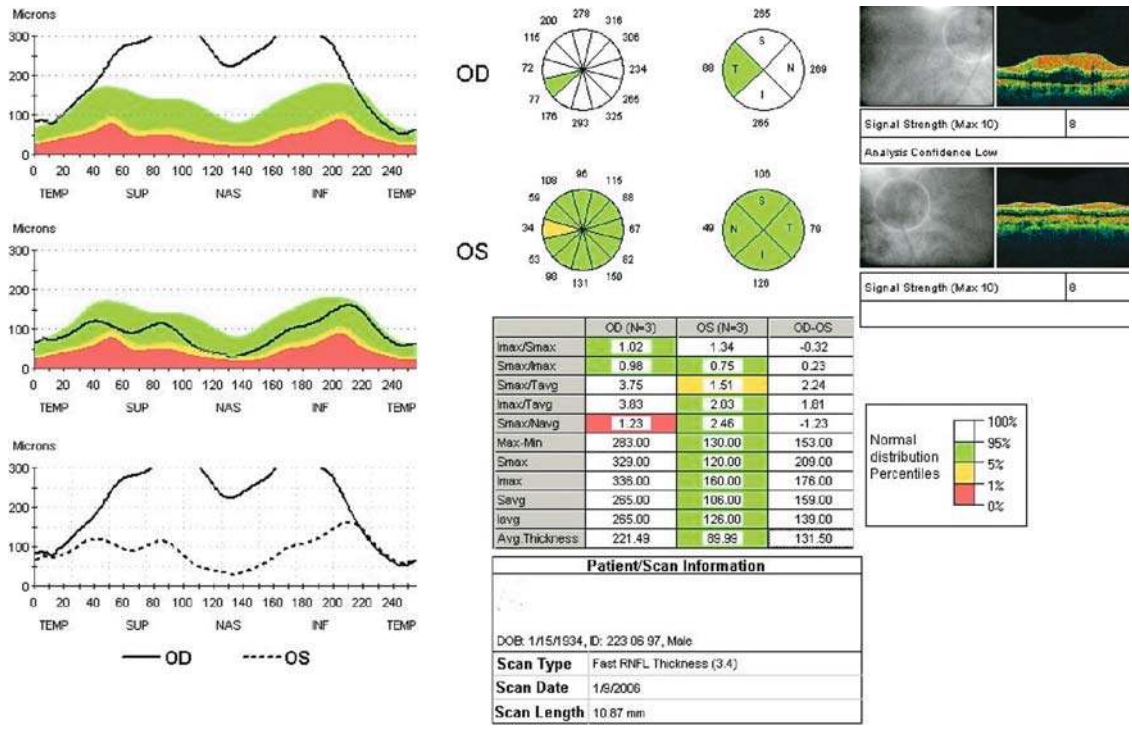
The Stratus OCT software (Carl Zeiss Meditec, Dublin, CA, USA) provides a variety of protocols for the evaluation of the retina. Various scanning techniques have been applied for the evaluation of optic nerve disorders.

Peripapillary Retinal Nerve Fiber Layer Scan (Fast RNFL Scan)

A 3.4-mm circular scan centered around the optic disc measures the peripapillary nerve fiber layer (NFL) thickness. The result is displayed "unwrapped," starting at the temporal side, followed by the superior, nasal, inferior, and finally back to the temporal side. Data are also shown in clock hours around the disc. A graph compares the measured peripapillary RNFL thickness with age-adjusted normative data[3] (Figure 10.1). Measurements falling within the green area of the graph represent the 5th to 95th percentile; those falling in the yellow area of the graph represent the 1st to the 5th percentile. The red area of the graph represents RNFL below the 1st percentile. Other numerical parameters include average NFL, maximal superior nerve fiber layer thickness, maximal inferior nerve fiber layer thickness, and a ratio of the previous two parameters.[3] This protocol is useful for the evaluation of optic atrophy or optic nerve edema (see Figure 10.1). The reproducibility of the Fast RNFL scan has been tested repeatedly in normal subjects and glaucoma patients with good results.[4–7] It is imperative that the scanning light be centered on the optic nerve during this test. If the thickest portions of the RNFL are not in their usual superior and inferior positions along the RNFL graph (if the two "humps" appear to be shifted to the right or left), one should suspect that the circular scan has not been centered on the optic disc and the data are not accurate.

Papillomacular Axis Line Scan

A 10-mm linear scan from the center of the fovea through the papillomacular bundle and optic nerve provides cross-sectional visualization of



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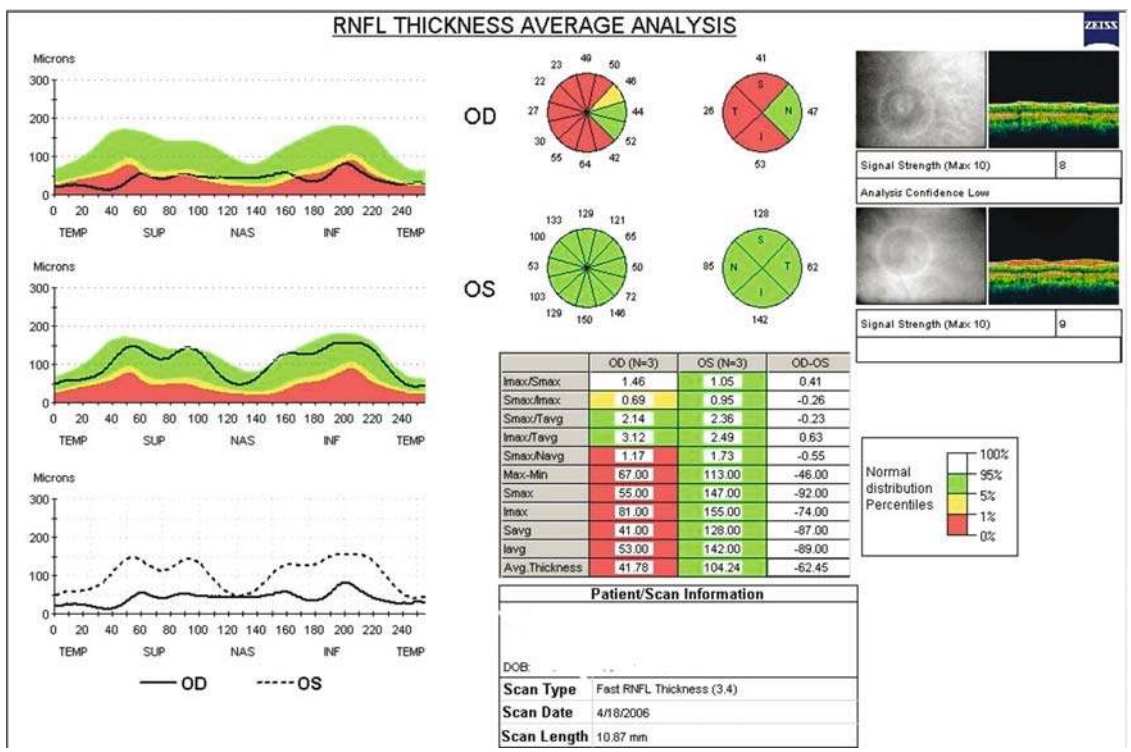

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FIGURE 10.1. Following resolution of disc edema **(A)** thinning of the RNFL below the first percentile is seen in all quadrants except the nasal one **(B)**.

the full thickness of the retina and optic nerve, with a 10-µm axial resolution (Figure 10.2A,B). This scan allows evaluation of the vitreo-retinal interface and individual retinal layers.[3] This protocol is useful for the evaluation of the optic nerve-retinal junction where subretinal fluid may accumulate in disorders such as optic nerve pits with subretinal fluid and central serous chorioretinopathy. Although the prelaminar optic nerve is visualized, imaging is limited by acoustic shadowing from the dentral retinal artery and vein. Optic disc drusen also cause shadowing that may not be distinguishable from blood vessels.

Optic Disc Analysis

Serial scans in a radial orientation centered on the optic nerve are useful for evaluating the profile of the optic disc and for comparing the

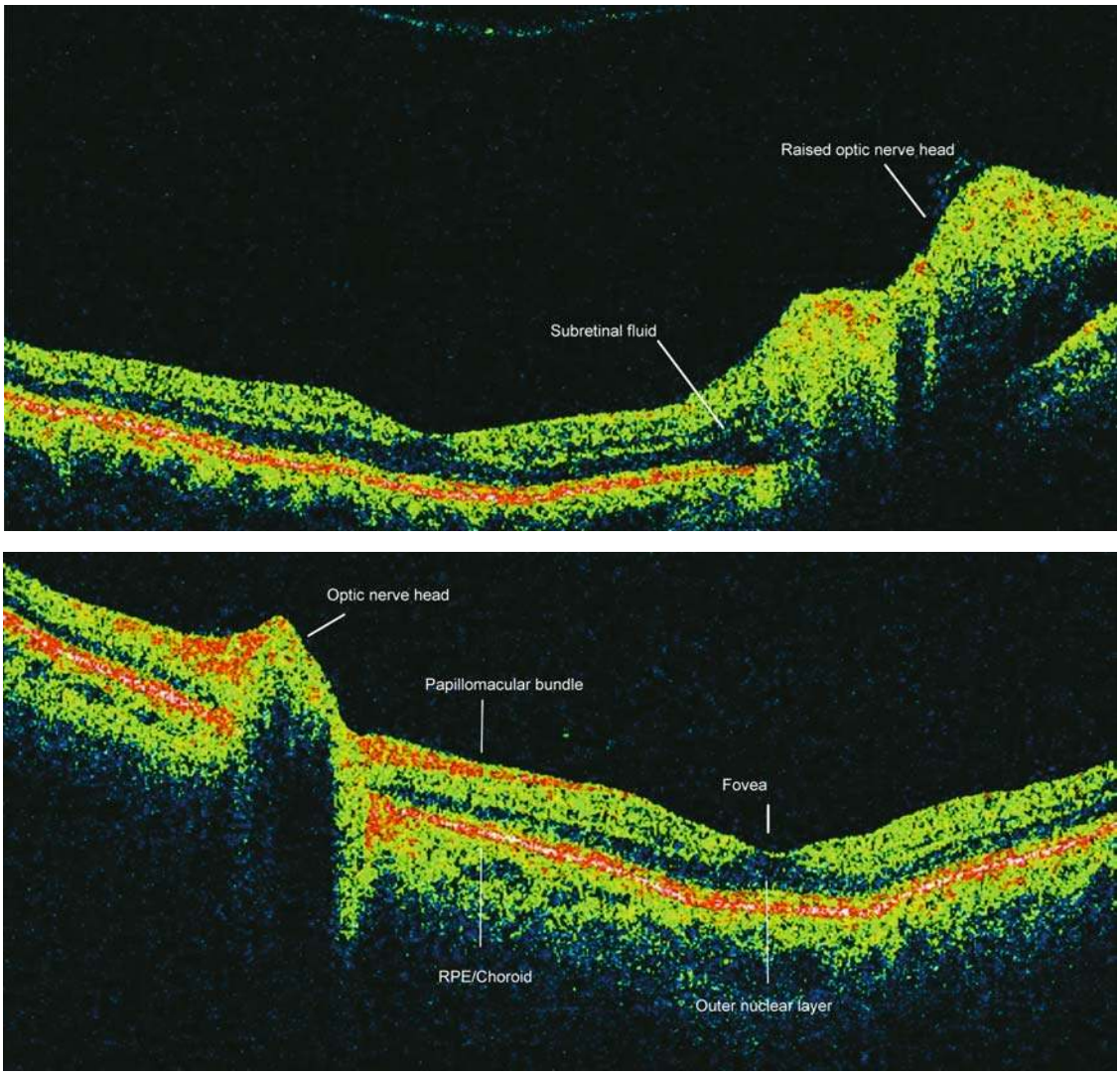


FIGURE 10.2. Papillomacular line scan in patient described in Figure 10.1. The right eye **(A)** shows elevation of the optic nerve head when compared to the normal left eye **(B)**. Also note some retinal edema at the retina–optic nerve junction, seen as a triangular zone of hyporeflectivity.

nerve fiber layer thickness in different planes. From this analysis, data of the optic nerve, disc area, cup area, and cup-to-disc ratio are calculated (Figure 10.3A,B).[3] Although this protocol was designed primarily for the evaluation of glaucoma,[4–8] it can be useful in the evaluation of congenital optic nerve anomalies, such as pits, drusen, or papilledema.

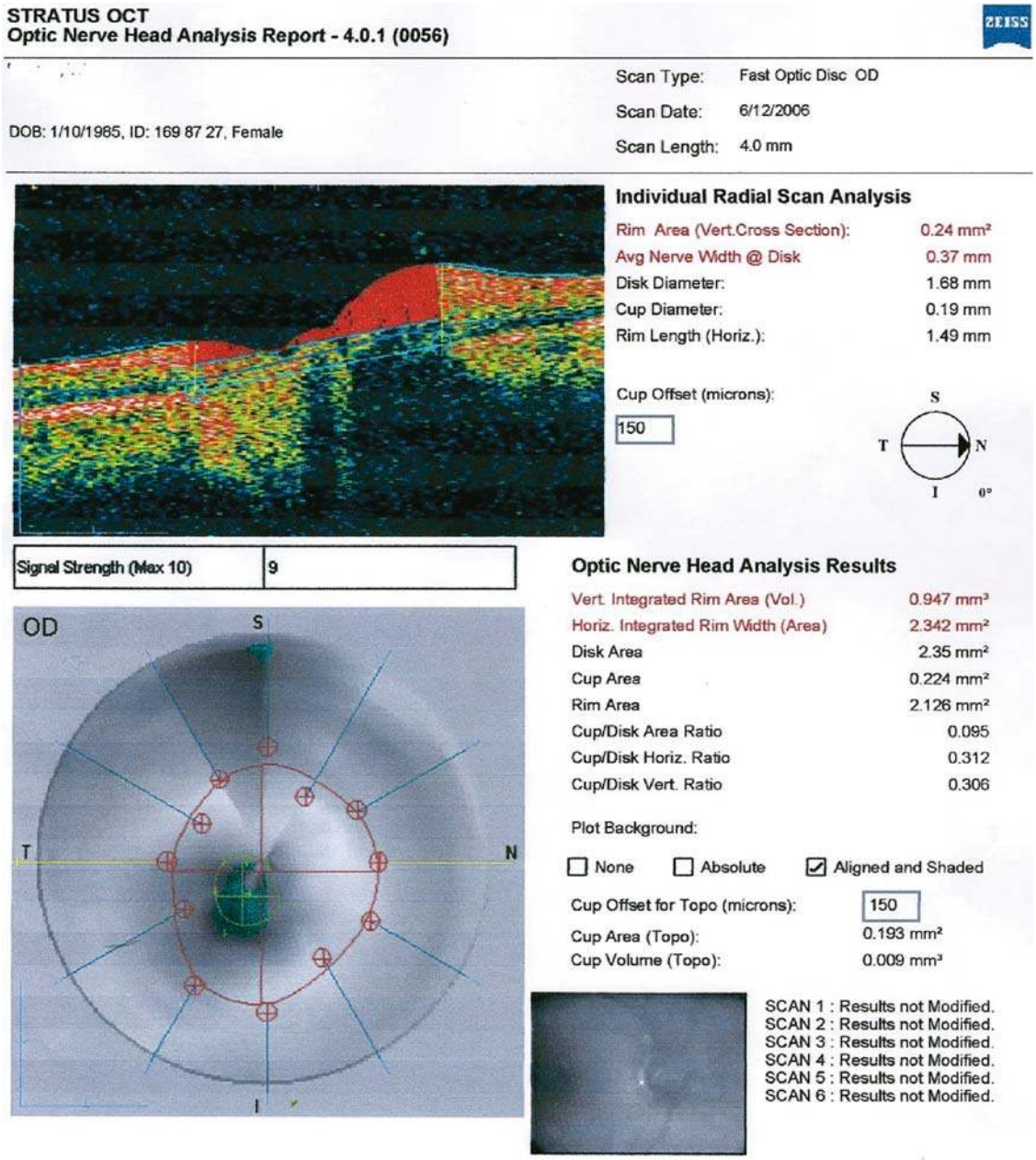
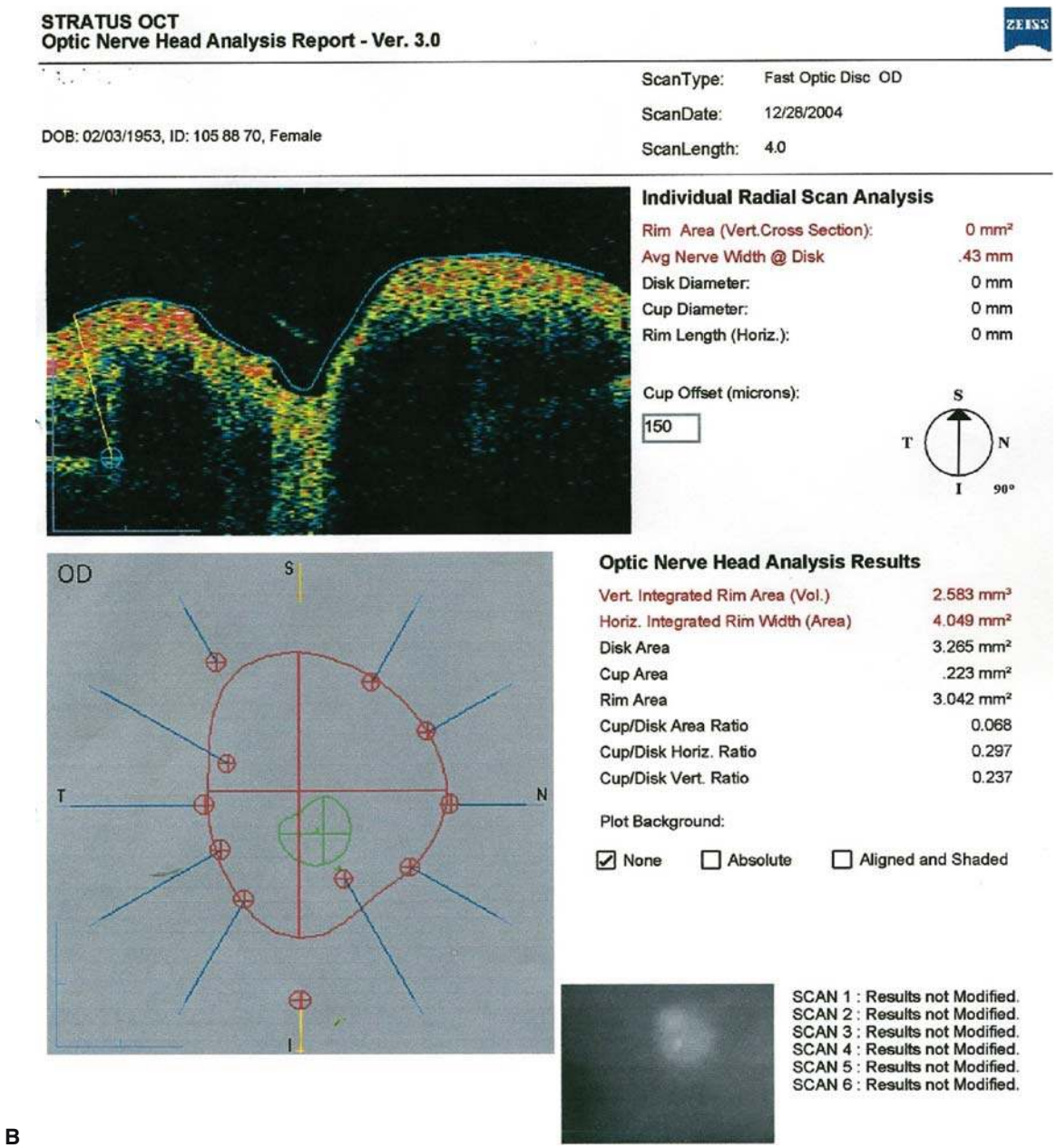


FIGURE 10.3. Optic disc analysis in a normal patient **(A)** and a patient with papilledema **(B)** showing differences in contour. Various parameters are provided by the protocol, such as vertical and horizontal cup/disc ratios, disc diameter, and cup diameter.



B

FIGURE 10.3. *Continued*

Macular Scans

This protocol not only provides a cross-sectional image through the fovea but also gives a macular thickness analysis. The macular scan can rule out macular changes missed on the papillomacular axis line scan (see foregoing) and can define macular disease that may mimic optic neuropathy,[3] including cystoid macular edema, pigment epithelial detachments, and subretinal fluid, which are visualized by this scan.

Optical Coherence Tomography in the Analysis of Optic Nerve Disorders

Using the peripapillary RNFL scan protocols already described, OCT can demonstrate RNFL atrophy secondary to ischemia, compression, demyelination, or increased intracranial pressure. Patterns of RNFL loss can be measured by OCT that may correlate with visual field defects. These patterns of RNFL loss may be useful in determining the location of lesions along the visual pathways. Peripapillary RNFL scans are also useful in documenting progressive changes or stability of lesions during follow-up.

Optic Disc Edema

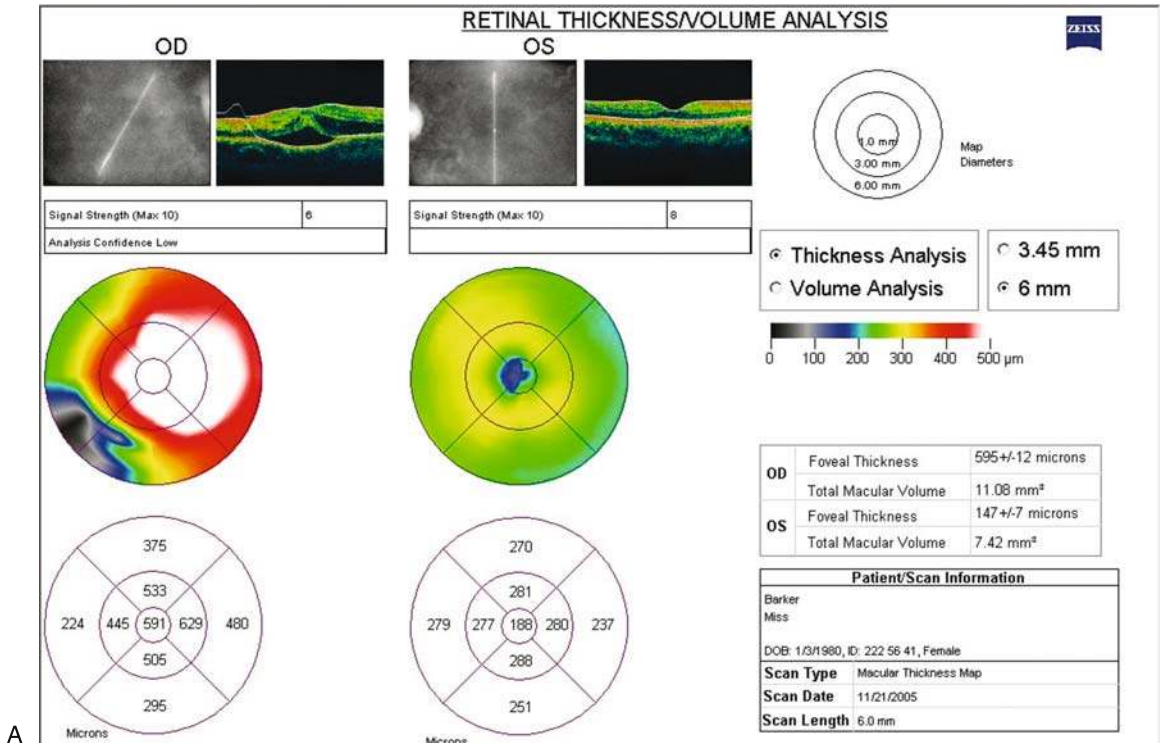
In the evaluation of optic disc edema from various causes, including papilledema, the combination of the peripapillary nerve fiber layer scan with the papillomacular line scan (see above) is useful. In cases of optic disc swelling, the peripapillary RNFL scan will show an increase in RNFL thickness that is above the 95th percentile of the normative data that are already included in the program. RNFL thickening can be sectoral, as in some cases of anterior ischemic optic neuropathy (AION), or diffuse, as in papilledema. Resolution of disc swelling is accompanied by a return to normal of the RNFL if no permanent damage has occurred, or a decrease below the 5th percentile if RNFL loss has occurred (see Figure 10.1A,B). Protocols for optic nerve analysis may also be applied in unilateral non-arteritic ischemic optic neuropathy (NAION) to evaluate the contralateral optic nerve for the "disk-at-risk" anatomy.

The line scan is useful for evaluating the presence of subretinal fluid that often accompanies optic nerve swelling in the peripapillary region and rarely in the subfoveal region, where it can cause central visual loss in some cases of papilledema from idiopathic intracranial hypertension.[9] Subretinal fluid can be documented and measured by OCT in other causes of disc swelling, such as papillophlebitis and NAION (in manuscript). The papillomacular line scan can also demonstrate apparent optic disc elevation from vitreopapillary traction.[10]

In papilledema, OCT can be used to objectively assess peripapillary nerve fiber layer swelling and to monitor its progression to resolution or atrophy (Figure 10.4). Optical coherence tomography, using the peripapillary RNFL scan, can also help to objectively distinguish normal subjects from patients with papilledema or pseudopapilledema by showing either evolution or resolution over time in cases of papilledema, or even no changes over time with pseudopapilledema. However, it cannot distinguish mild papilledema from pseudopapilledema with a single measurement, because patients with congenitally crowded, pseudopapilledematous optic nerves have slightly thicker than normal RNFL, unless optic disc drusen develop,[11] which would be associated with RNFL thinning.

Optic Atrophy

Optical coherence tomography can help rule out nerve damage, and, when normal, it allows clinicians to redirect their attention to the retina or anterior segment as the site of unexplained visual loss. In optic disc atrophy, OCT can objectively measure loss of RNFL caused by ischemic, compressive, or hereditary, nutritional, or toxic optic neuropathies. In glaucoma, loss of RNFL, as measured by OCT, has been shown to correlate with disease progression as measured with automated perimetry.[12] This finding can be extrapolated to other causes of optic



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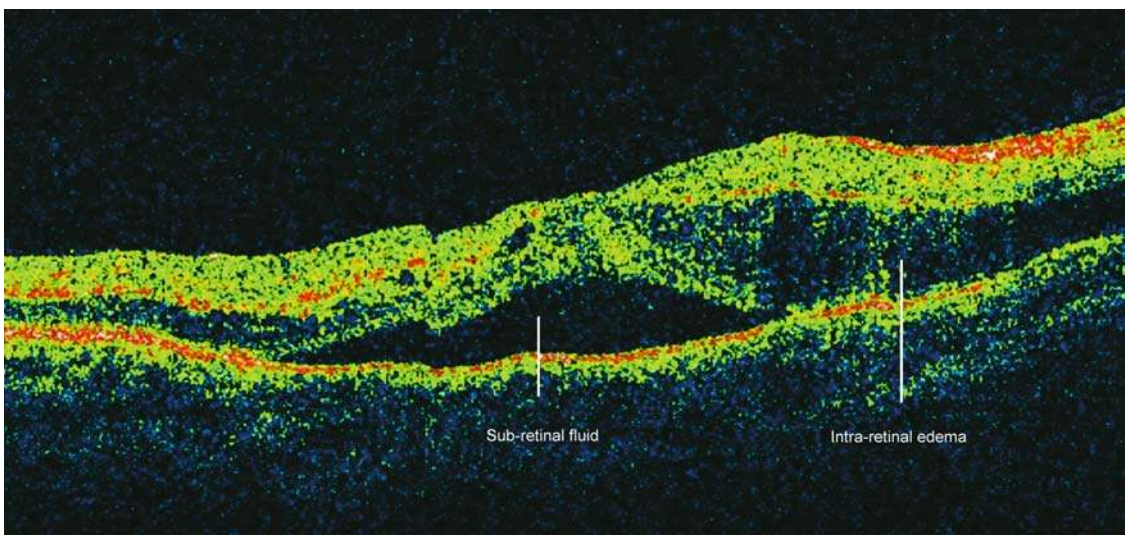

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FIGURE 10.4. **(A)** Line scan in a patient with subretinal fluid secondary to papillophlebitis. **(B)** Note the swollen disc contour, as well as the area of hyporeflectivity under the fovea that represents subretinal fluid.

atrophy resulting from pregeniculate disease, where RNFL measurements correlate well with visual field defects, which may help localize lesions in the visual pathways, especially if the visual fields are unreliable.

In patients with compressive lesions, OCT can play a role in surgical management. It can be used to monitor progression of optic neuropathy in patients with meningiomas or to assess prognosis. For example, in cases of thyroid

compressive optic neuropathy, normal RNFL measurements may indicate a favorable post-decompression visual prognosis. In band atrophy caused by compressive chiasmal lesions, OCT has shown a decrease in RNFL thicknesses in the nasal and temporal quadrants, as well as in the overall average RNFL thickness, that corresponds with the measured visual field loss.[13,14]

In acute Leber's hereditary optic neuropathy (LHON), OCT confirms that the average RNFL is thicker than normal. OCT has also shown markedly reduced RNFL in atrophic LHON. Among patients in whom visual recovery occurs in the atrophic stage, the average RNFL thickness has been reported to be increased compared to patients without recovery.[15] Exceptions to this occurrence have been observed in our practice. Unaffected carriers of the LHON mutation have also been found to have thicker temporal RNFL than controls in one study.[16] This finding also has yet to be confirmed.

In toxic optic neuropathy from ethambutol, OCT has shown a significant loss of nerve fiber layers in the temporal quadrant that is consistent with papillomacular bundle damage. The severity of RNFL loss is proportional to the visual prognosis, with more severe loss suggestive of chronic visual field loss.[17]

Optical coherence tomography has a possible role in the evaluation of disease progression in multiple sclerosis (MS). A recent study found decreased RNFL thickness in eyes of patients with optic neuritis secondary to MS and with MS without history of optic neuritis when compared to controls. This decrease in RNFL correlated with decrease in visual function as measured by low contrast letter acuity or contrast sensitivity.[18] Based on this study, OCT may serve as a biomarker for disease activity that may assist in the evaluation of new therapies for demyelinating disease.

Optic Nerve Anomalies

In the evaluation of optic nerve anomalies, OCT can show features that are particular to each condition. In buried optic disc drusen, OCT of the optic nerve can demonstrate shadowing.[19] In eyes with optic nerve head drusen, OCT can detect NFL thinning that correlates with visual field loss secondary to drusen.[20] OCT may be helpful in monitoring patients who have optic disc drusen combined with increased intraocular pressure.[22] In the morning glory anomaly, OCT can show a lacy pattern of cavitation in the anterior portion of the optic nerve head.[19] Myelinated nerve fibers appear as thickened nerve fiber layer on OCT in affected areas of the retina.[19] In superior segmental optic hypoplasia, OCT is associated with thinning of the superior peripapillary RNFL as well as the foveal RNFL. OCT can, therefore, help detect minimal degrees of hypoplasia.[19,22]

Optical Coherence Tomography in the Evaluation of Occult Retinal Disease

A discussion on the role of OCT in the diagnosis of retinal disease is extensive and beyond the scope of this chapter. However, of great interest to the neuro-ophthalmologist are retinal diseases that mimic optic nerve disease. OCT can demonstrate subtle areas of subretinal fluid, subretinal membranes, retinal thinning (holes), and preretinal membranes that might be difficult to identify or confirm by ophthalmoscopy or fluorescein angiography. To help differentiate retinopathy from optic neuropathy and identify occult retinopathy, macular scans can reveal subtle abnormalities such as macular edema, serous detachment, and pigment epithelial detachment.

A typical example of the utility of OCT in detecting retinal disease that mimics optic neuropathy is central serous retinopathy. Central serous retinopathy can usually be diagnosed by ophthalmoscopy and easily confirmed by fluorescein angiography. However, there are rare cases where OCT can show small collections of subretinal fluid that may not be seen clinically. Furthermore, OCT can be done quickly through an undilated pupil. The differentiation of central serous retinopathy from recurrent optic neuritis is important in MS patients who may experience acute visual loss while receiving corticosteroids.[23]

OCT can also be useful in the evaluation of toxic maculopathies that may be mistaken for optic neuropathies. For example, visual loss related to submacular fluid, rather than an optic neuropathy, may be distinguished by OCT in cisplatin retinopathy.[19] In hydroxychloroquine retinopathy, OCT has demonstrated disruption of the photoreceptor inner/outer segment junction as well as thinning of the outer nuclear layer in severely affected patients (in manuscript). In chronic progressive eye conditions, such as retinitis pigmentosa, or after eye surgeries, such as cataract extraction, OCT can document the development of cystoid macular edema and differentiate the acute visual loss from a recent optic nerve lesion.

Conclusion

Optical coherence tomography is a new technology that allows in vivo imaging and measurement of retinal and optic nerve anatomy. For the neuro-ophthalmologist, it can provide objective measurement of the peripapillary nerve fiber layer and measure optic nerve characteristics such as the cup-to-disc ratio. It can also help prove that retinal disease is the cause of visual loss. Research prototype instruments are presently improving the resolution of optical coherence tomography.[24–28] With better resolution, an even greater expansion in the application of this instrument will be seen in the future.

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11
The Use of Multifocal Electroretinograms and Visual Evoked Potentials in Diagnosing Optic Nerve Disorders

Donald C. Hood and Karen Holopigian

Electrophysiological tests of vision measure the electrical activity generated by the eye, the optic pathways, and the visual cortex, and thus provide important diagnostic information to the clinical ophthalmologist. Traditionally, these electrophysiological tests involved stimulation of relatively large areas of the retina.[1] For example, for the standard electroretinogram (ERG) and the flash visual evoked potential (VEP) tests, the entire retina is illuminated. Other tests, such as the pattern ERG and VEP tests, use a stimulus that typically exceeds 15° in diameter. The size of the stimuli used for these tests presents a problem if the clinician is interested in the local topography of the damage to the retina or optic nerve, as is often the case in neuro-ophthalmology. Although ERG and VEP responses can be elicited to relatively small stimuli using traditional measures, each retinal area had to be be tested separately. Thus, if a clinician wanted a topographical map, the time needed to obtain multiple responses was prohibitive. The multifocal technique was devised to solve this problem.[2] With both the multifocal ERG and VEP techniques, local responses are recorded simultaneously from many regions of the visual field. These local electrophysiological measures can be combined with visual fields obtained with static automated perimetry (SAP) that assess corresponding retinal areas. Together, these multifocal tests allow the clinician to rule out nonorganic causes of vision loss, rule out retinal (i.e., preganglion cell) causes, and, in some cases, distinguish among diseases of the ganglion cells/optic nerve. This chapter provides an introduction to these techniques and focuses, in particular, on the use of these techniques in diagnosing optic nerve disorders.

The Multifocal Electroretinogram

The standard ERG is a massed potential, the result of the summed electrical activity of the cells of the retina. With the multifocal technique, many local ERG responses can be recorded from the cone-driven retina in minutes. Although the multifocal technique is relatively new, it is widely used to diagnose and study retinal diseases.[3] Before describing how the multifocal electroretinogram (mfERG) can be of use in diagnosing optic nerve disease, it is necessary to understand some of the basics of how it is recorded and which retinal components contribute to the responses.

Recording the mfERG

Typically, the multifocal stimulus is displayed on a computer monitor, although new display technologies are beginning to be employed.[4] The display contains an array of hexagons; the most commonly used displays contain either 61 or 103 hexagons (Figure 11.1A,B shows the

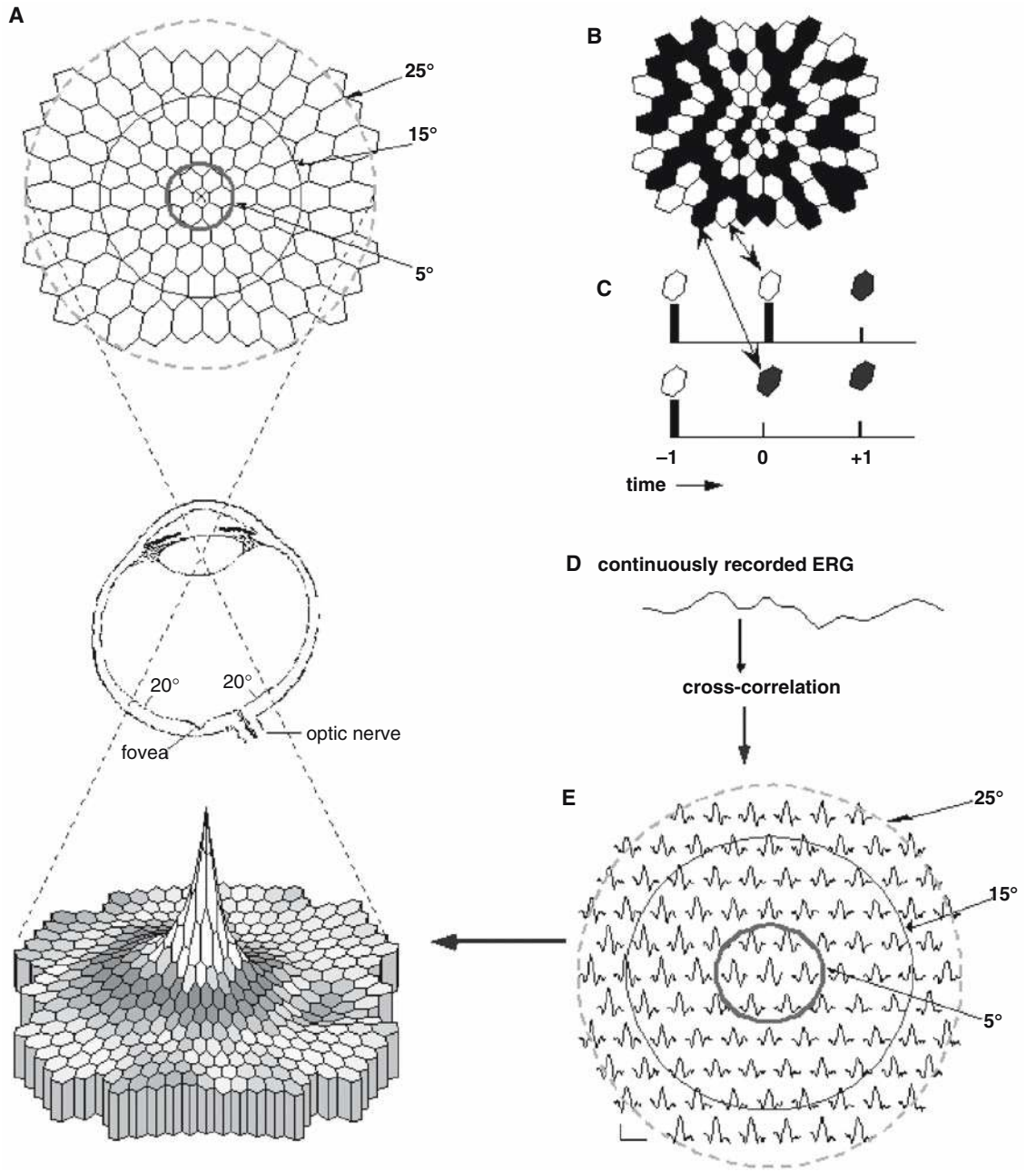

FIGURE 11.1. The multifocal electroretinogram (mfERG). **(A)** *Top:* An mfERG display with 103 scaled hexagons. *Circles* have been drawn to indicate radii of 5° (*thick dark gray*), 15° (*thin black*), and 25° (*dashed light gray*). *Middle:* A schematic of the eye illustrating where the image of the display falls. *Bottom:* The three-dimensional (3D) density plot of the responses **(E)** from a control subject's right eye. **(B)** The mfERG display at one moment in time. **(C)** The stimulation sequence of two sectors in **B**. **(D)** The single continuous ERG record generated by the display. **(E)** The 103 mfERG trace array. The responses (first-order kernels) are extracted by correlating the stimulus sequence **(C)** with the continuous ERG record **(D)**. (Reprinted from Hood et al.,[9] with permission from Lippincott Williams & Wilkins.)

103-hexagon array). The hexagons are usually scaled with eccentricity so as to produce local ERG responses of approximately equal amplitude in individuals with normal vision.[2] The retinal size of the display varies across laboratories and clinics but is generally 40° to 50° in diameter. There are guidelines concerning recommended stimulus and recording parameters.[5]

When the recording starts, the display (Figure 11.1B) appears to flicker because each hexagon goes through a pseudorandom sequence of black and white presentations (Figure 11.1C). With the same electrodes and amplifiers used for standard, full-field ERG recordings, a single continuous ERG record is obtained (Figure 11.1D). The continuous record is typically 4 to 8 min in length but is obtained in 15- to 30-s segments for the subject's comfort (Figure 11.1D). Technically, the mfERG responses are derived as the first-order kernels of the cross-correlation between the stimulation sequence and the continuously recorded ERG. Further details have been published.[2,3,5,6] The recording is done with a contact lens- or thread-type electrode, usually with the pupil dilated. The 103 mfERG responses from the right eye of a control subject are shown in Figure 11.1E. Notice that the responses are similar in waveshape and amplitude as a function of eccentricity.

Presentation of the mfERG Responses

The responses in Figure 11.1E are positioned so that they do not overlap. Therefore, the scaling is not linear as a comparison of the iso-degree circles in Figure 11.1A and 11.1E indicates. The trace array in Figure 11.1E is the most common, and often the most useful, way to display the results. For some analyses, the sum or average of the responses within various regions of the display are more informative. For example, responses within rings around fixation may be examined. In Figure 11.2B, the responses from Figure 11.1E are grouped by rings and the amplitudes are summed (Figure 11.2A). The responses become larger with eccentricity because progressively larger areas of the retina are stimulated. Another approach takes retinal area into consideration. In particular, the amplitude of the summed response is divided by the total area of the hexagons in the associated ring. The resulting responses (Figure 11.2C) are expressed as a measure of response amplitude per unit area (response density in nV/deg^2). As expected, the response per unit area is highest in the fovea. Although this analysis by rings is useful for many purposes, it is not an appropriate display for summarizing the effects of retinal diseases that have nasotemporal asymmetries. However, the commercial software allows for arbitrary groupings of responses so that regional response densities can be compared.[6–8]

The mfERG results can also be displayed in a three-dimensional (3D) plot, an example of which can be found at the bottom of Figure 11.1A. For the 3D plot, at each point the response amplitude is divided by the area of the hexagon (i.e., a response density is obtained for each hexagon). Notice that there is a depression associated with the optic disc and a peak associated with the fovea. Because the 3D plots can be misleading, it has been advised that they should never be presented without the associated trace arrays.[3,5,9,10] For example, it is possible to see a peak in a 3D plot when there is no recordable signal present. On the other hand, because the foveal peak and optic disc depression can be seen in the 3D plot, it can be useful for assessing the location of fixation.[3,9]

Measuring Latency as Well as Amplitude

When analyzing mfERG responses for abnormalities, it is important to examine both the amplitude and the timing (latency) of the responses. In some diseases, damage to the outer retina can result in mfERG responses of reasonably normal amplitudes but with markedly delayed timing.[3] For example, large delays have been observed in patients with retinitis pigmentosa (RP),[11–13] cone rod dystrophy (CRD),[3] cone dystrophy,[14] diabetic retinopathy (DR),[15–17] and occult macular dystrophy.[18] Figure 11.3 shows records from patients with DR, RP, and CRD. If the waveforms are examined closely, it is apparent that they are all delayed as compared to the normal control (Figure 11.3, upper left panel). Although both

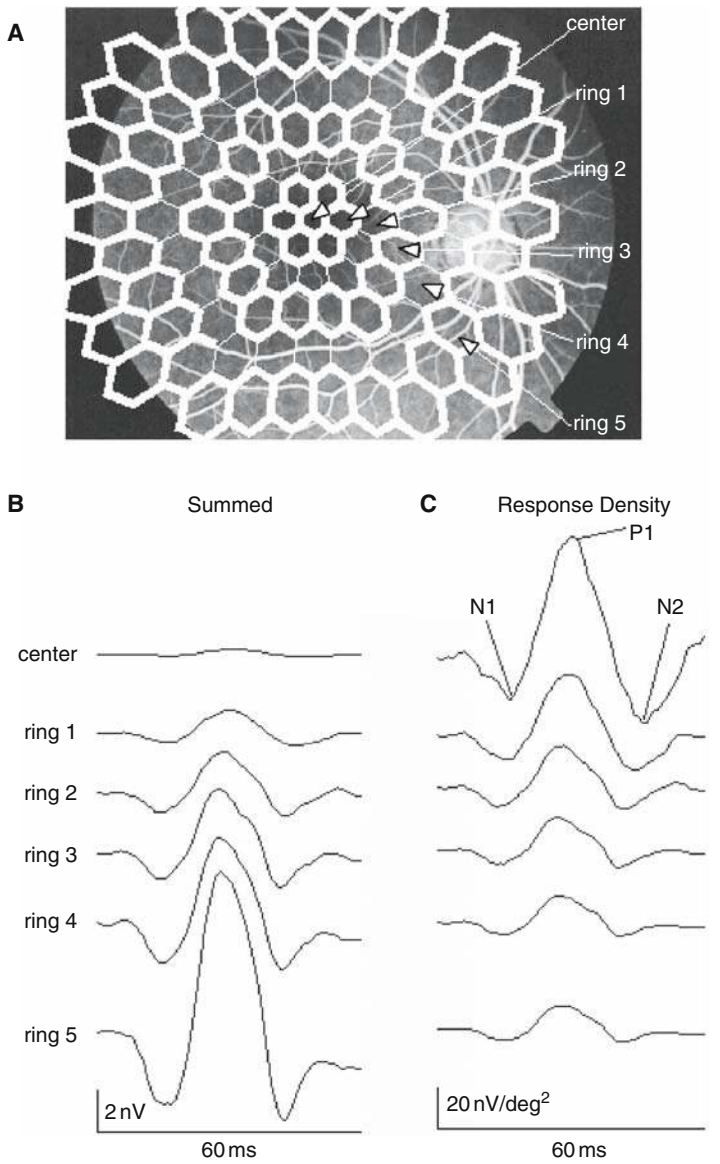

FIGURE 11.2. The mfERG in relationship to retinal anatomy. **(A)** The mfERG stimulus overlaid on top of a fundus photograph. The sectors are grouped by *rings* around the center and marked by *arrows*. **(B)** The summed mfERG responses for each of the rings marked in **A**. **(C)** The same responses as in **B** but expressed in units of response density (nV/deg^2). That is, the summed responses in **B** are divided by the total area of stimulation in the associated rings. The principal mfERG components *N1*, *P1*, and *N2* are labeled for one of the responses. (Reprinted from Hood et al.,[9] with permission from Lippincott Williams & Wilkins.)

commercial and specialized software[19] provides measures of latency, restricting the time scale so only the first portion of the response is displayed allows for an easy analysis of latency changes; this is demonstrated in Figure 11.4, where the first 35 ms of the records from a control subject and from a patient with RP are presented. Notice that the responses from the

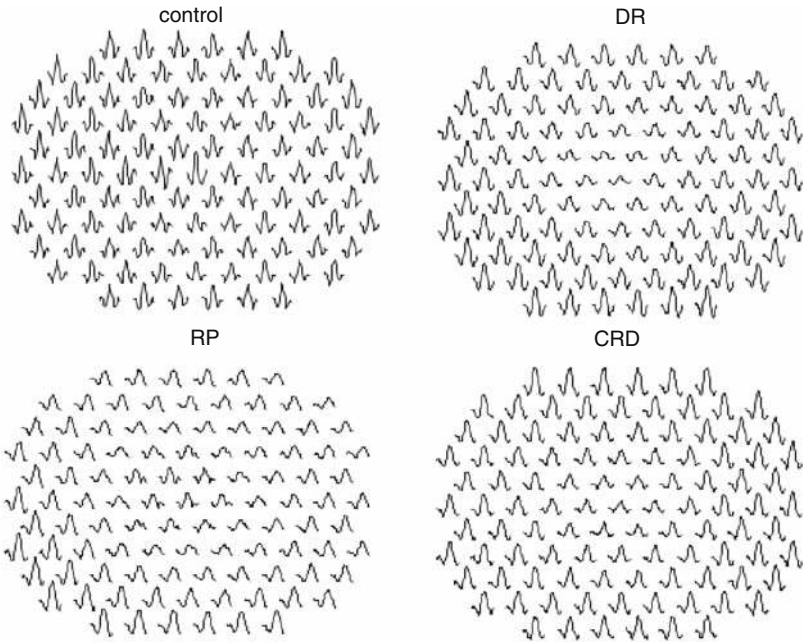

FIGURE 11.3. Examples of mfERG trace arrays for 103 hexagons. *Upper left:* Results from a control subject. *Upper right:* Results from a patient with *DR* and cystoid macular edema (CME). *Lower left:* Results from a patient with *RP*. *Lower right:* Results from a patient with *CRD*. The responses from the patients are delayed, relative to the results from the control subject.

patient with RP appear to be truncated because they have not yet reached their peak amplitude at 35 ms. The responses from the control subject, however, have reached the maximum response and are decreasing in amplitude by 35 ms. These results demonstrate the differences in implicit time between the control subject and the patient with RP.

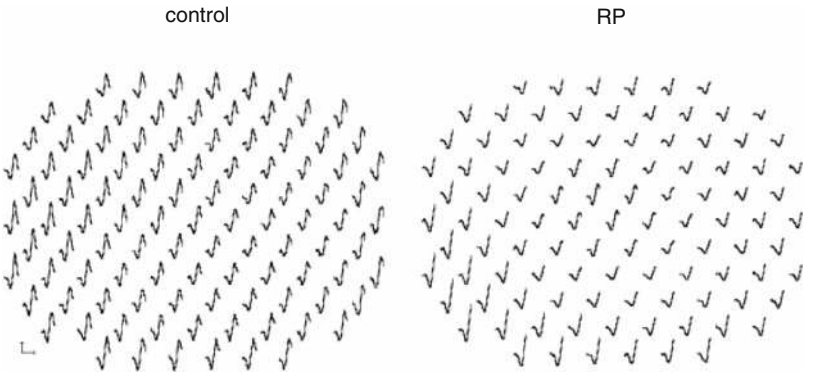

FIGURE 11.4. The mfERG responses are shown on a time axis from 0 to 35 ms, showing the delayed responses from the patient. *Left:* Results from a control subject. *Right:* Results from a patient with *RP*. (Reprinted from Hood,[3] with permission from Elsevier.)

Generation of mfERG in the Outer Retina

The mfERG, similar to the standard full-field ERG, has only a relatively small contribution from retinal ganglion cells under standard recording conditions.[3,8] (Note that the term "standard recording conditions" refers to a fast flicker sequence as in Figure 11.1C where the individual hexagons have a probability of 50% of being white or black on every frame change.) In fact, in primates the standard mfERG is largely shaped by bipolar cell activity, with smaller contributions from the photoreceptor and inner retinal (e.g., amacrine and ganglion) cells.[20] Thus, the standard mfERG provides a measure of the health of the outer retina (i.e., cone photoreceptors and bipolar cells) and can be used to help distinguish between diseases of the outer retina (i.e., before the ganglion cells) and diseases of the ganglion cells and/or optic nerve.

The mfERG and the Diagnosis of Retinal and Optic Nerve Disorders

For a number of years, our laboratory has been recording standard mfERGs from patients from the practice of two neuro-ophthalmologists (Drs. M. Behrens and J. Odel). Here we summarize the most common uses of the mfERG in diagnosing optic nerve disorders in a neuro-ophthalmologic practice. (For more examples, see Hood et al.[9])

Ruling Out Diseases of the Outer Retina

A common task facing the neuro-ophthalmologist is deciding whether a visual defect is caused by a disorder of the optic nerve or a disorder of the outer retina. A normal mfERG recording can be used to rule out outer retinal disease, whereas an abnormal mfERG recording, especially when the defects correspond to abnormal areas of the visual field, identifies an outer retinal origin of the problem. Here are two examples.

Figure 11.5A shows the visual fields of a 16-year-old girl who complained of difficulty in reading. Her full-field ERG was normal and she had a normal fundus examination; therefore, a retinal expert suspected the correct diagnosis was optic neuritis. Her standard mfERGs, however, showed depressed responses in the central regions (Figure 11.5B). Based upon these recordings, her disorder was diagnosed as being retinal in origin.

It is important to emphasize that it is essential to compare the mfERG findings to the results from visual fields. Normal variations, as well as fixation errors (see following), may produce mfERG responses that are reduced in amplitude, relative to normal. Consider the patient in Figure 11.5. To aid in comparing the visual field and mfERG topographies, iso-degree contours (circles) have been added to the figures. Although more sophisticated procedures for comparing visual fields to the mfERG exist,[21] these contours are sufficient for most clinical purposes. The records in Figure 11.5C show the mfERG responses averaged (response density; see Figure 11.2C) within the central 5°, between 5° and 15°, and between 15° and 25°. The agreement between the depressed amplitudes of the mfERG (see Figure 11.5B,C) and the regions of the visual fields showing a defect (see Figure 11.5A) confirmed that the problem is retinal in origin. The mfERG, reduced in amplitude, but relatively unchanged in implicit time, resembles those seen in Stargardt's disease.[22]

This patient illustrates a problem often facing clinical ophthalmologists and neuro-ophthalmologists, that of differentiating optic nerve from retinal dysfunction in patients with an unexplained loss of central vision but with a normal fundus exam. In some cases, the unexplained loss can be paracentral, as in the case shown in Figure 11.6. This patient was a 41-year-old male engineer who reported that, although his vision in his right eye was normal, he saw a "smudge" in the vision of his left eye. His fundus appeared normal, and his visual acuity was 20/20 in both eyes. His visual fields (Figure 11.6A), however, showed paracentral ring scotomas in both eyes. Both glaucoma and a retinal abnormality were possible diagnoses. Both the trace arrays (Figure 11.6B) and the responses averaged by rings (Figure 11.6C) show reduced mfERG amplitudes in regions corresponding to his visual field defects. Based upon these records, it was concluded that the

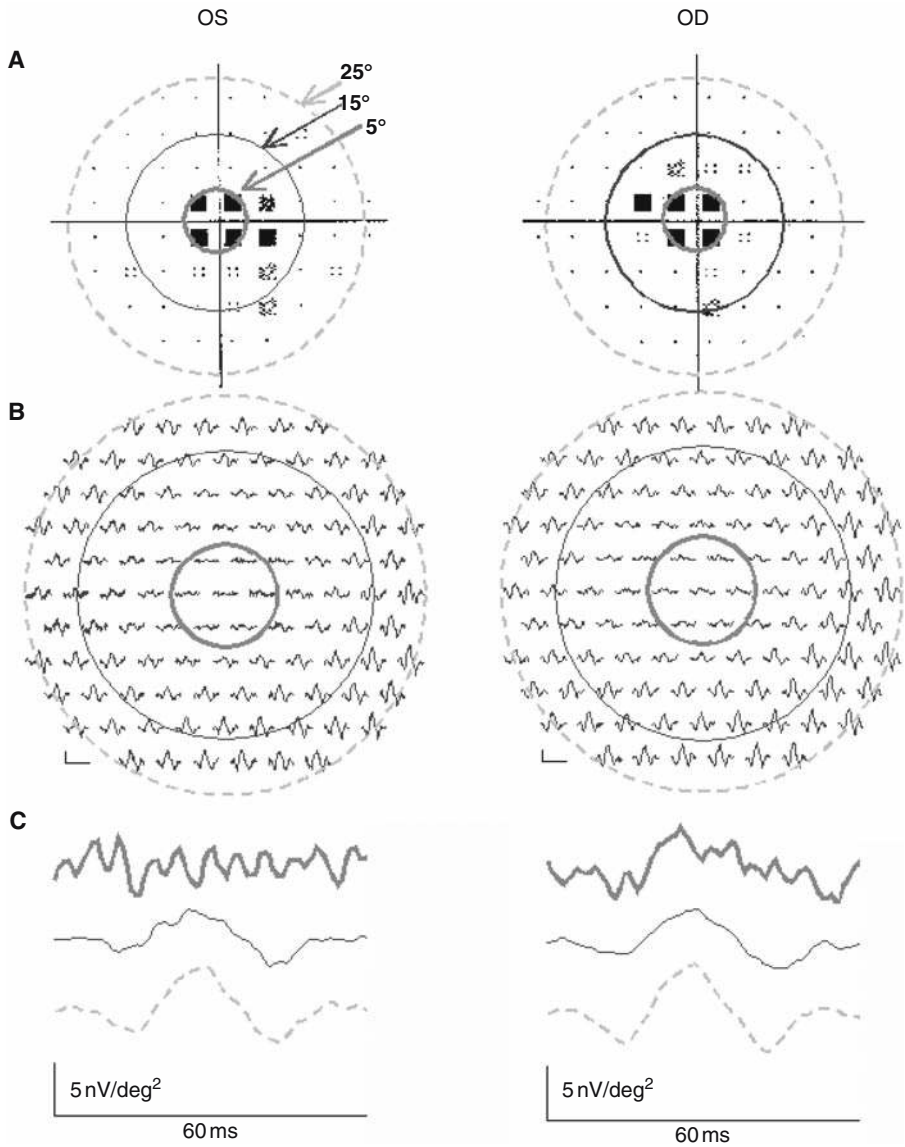

FIGURE 11.5. Humphrey visual fields and mfERGs for the right (*right side*) and left (*left side*) eyes of a patient with Stargardt's disease. **(A)** 24–2 Humphrey visual fields (total deviation probability plots) show abnormal thresholds for the central areas. **(B)** The mfERG responses show reduced central amplitudes, but relatively unchanged implicit times, typical of early Stargardt's disease. *Vertical and horizontal calibration bars* indicate 100 nV and 60 ms, respectively; *thick dark gray*, *thin black*, and *dashed light gray circles* indicate radii of 5°, 15°, and 25°, respectively. **(C)** The amplitudes for the three rings shown in **B** are plotted as response densities. (Modified from Figure 6 in Hood.[10])

visual problem derived from a retinal abnormality. Subsequent studies revealed abnormal antibody activity suggestive of melanoma-associated retinopathy (MAR) in this patient, confirming the retinal origin of the problem.

The Problem of Fixation Errors

One of the most common mistakes made with the multifocal ERG is attributing an abnormal result to a retinal problem when it is actually

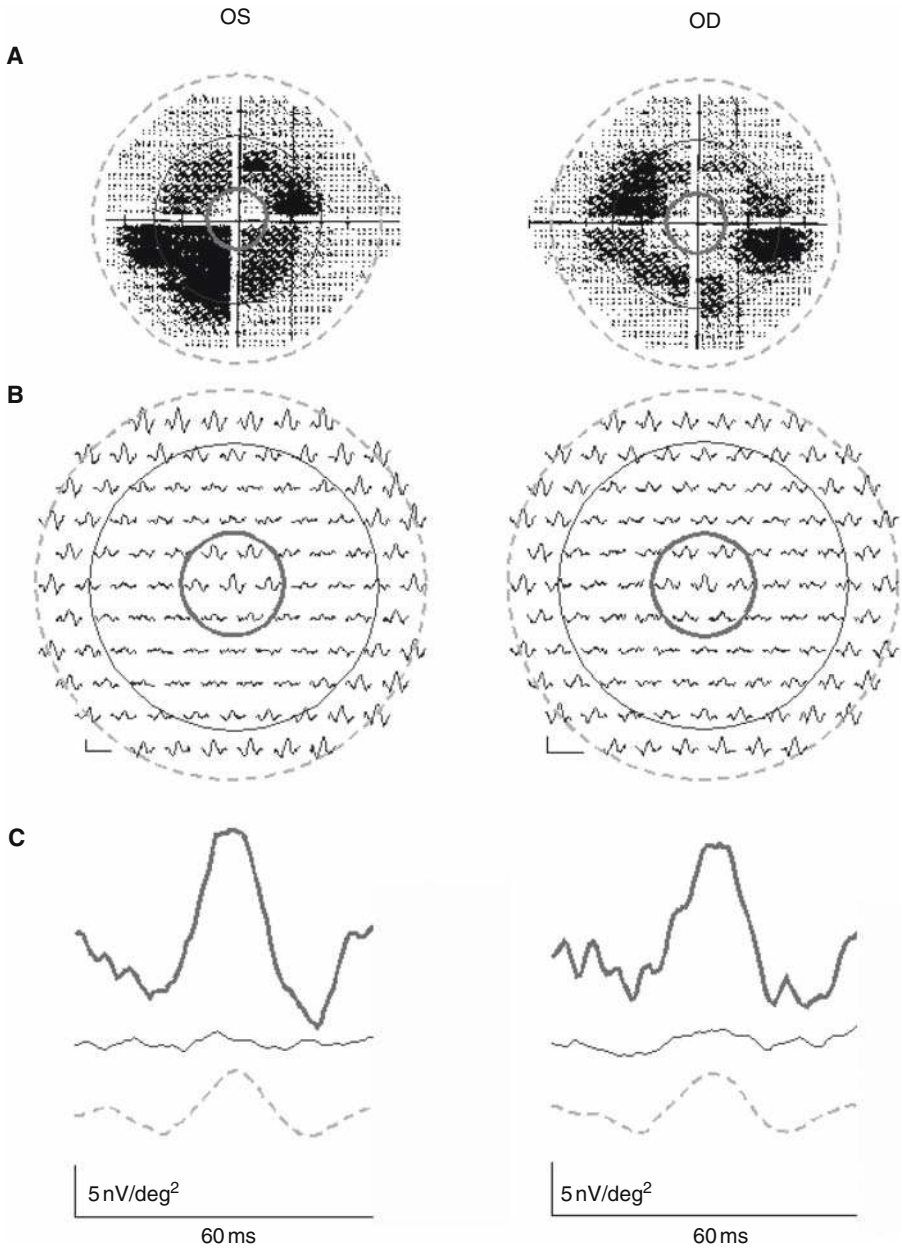

FIGURE 11.6. Humphrey visual fields and mfERGs for the left (*left side*) and right (*right side*) eyes of a patient with suspected MAR. **(A)** 24–2 Humphrey visual fields show abnormal thresholds for parafoveal regions. **(B)** The mfERG responses show the same pattern of parafoveal loss as in the visual field. *Vertical and horizontal calibration bars* indicate 100 nV and 60 ms, respectively; *thick dark gray*, *thin black*, and *dashed light gray circles* indicate radii of 5°, 15°, and 25°, respectively. **(C)** The amplitudes for the three rings shown in **B** are plotted as response densities. (Modified from Figure 6 in Hood et al.[11].)

the result of a fixation problem. The results in Figure 11.7 illustrate this point. The patient, a 64-year-old woman, complained of a loss of vision in her right eye. Her mfERG showed a decrease in response amplitude in the central 5° (Figure 11.7B). The patient's visual acuity was 20/400 OD and she could not see the fixation target, but her fixation was monitored with an infrared camera and appeared steady. However, whenever the macular area is potentially involved and/or there is any question about the patient's ability to fixate steadily, the accuracy of fixation must be determined. There are two relatively easy ways to do this using the mfERG

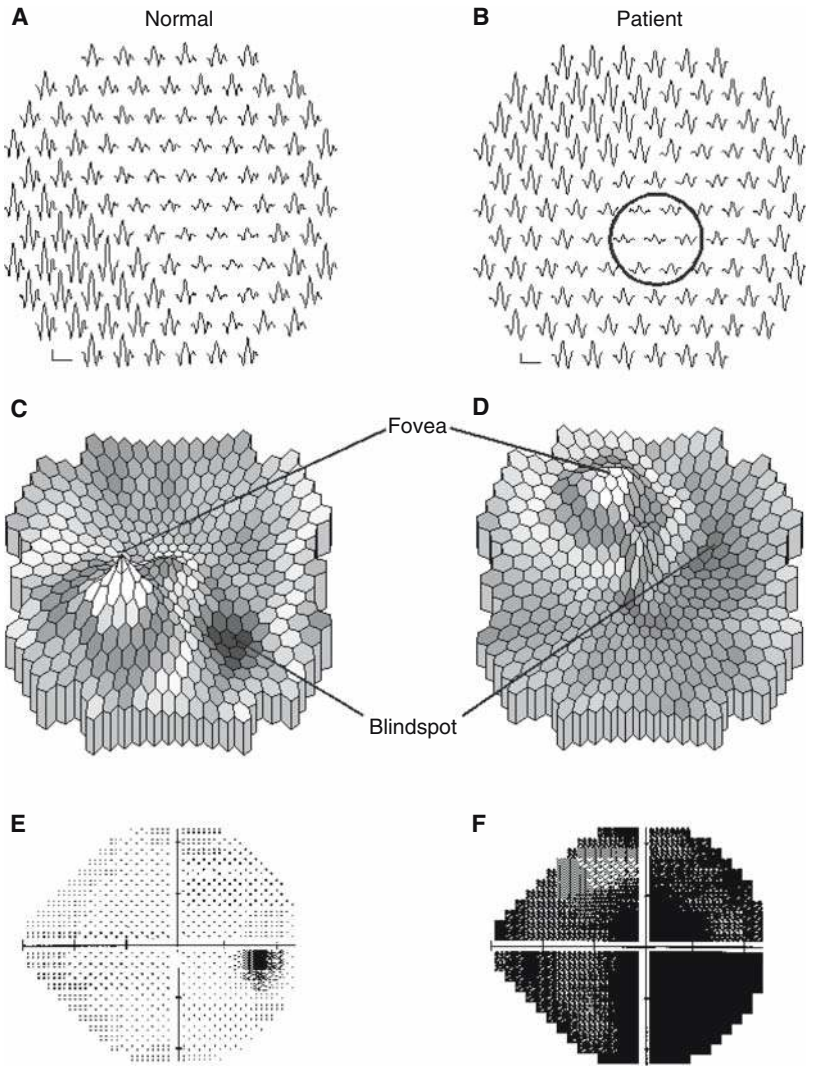

FIGURE 11.7. The problem of eccentric fixation. **(A)** mfERG from a control subject instructed to fixate at a target 8.5° down and to the left of center. **(B)** mfERG from a patient. *Black circle* indicates an area of apparently decreased mfERG responses resulting from fixation error. **(C)** 3D plot for the mfERG in **A**. **(D)** 3D plot for the mfERG in **B** of the patient. The reduced amplitudes in the patient's mfERG are likely caused by eccentric fixation and not retinal damage. **(E)** Visual field from the control subject. **(F)** Visual field from the patient. (Modified from Figure 14 in Hood et al.[11])

records. First, compare the mfERG responses to the visual field. In this case, her field depression extended at least to 25° (Figure 11.7F) and clearly did not agree with the location of the depression of the mfERG (circle in Figure 11.7B). Based on this evidence alone, the hypothetical retinal deficit in this patient should be considered suspicious. Second, the 3D plot in Figure 11.7D can be examined. Notice that both the foveal peak and the optic disc depression are displaced compared to the 3D plot from the control subject with normal fixation (see Figure 11.1A, bottom). The patient appears to be fixating eccentrically, and all the apparent abnormalities seen in the trace array in Figure 11.7B are based on poor fixation. The left column of Figure 11.7 illustrates the point. Here an individual with normal vision was asked to fixate down and to the left 8.5° from the center. Notice how the pattern of the patient's mfERG resembles that of the results from the control in Figure 11.7A and 11.7C, except that the patient was fixating up and to the left of the target.

Figure 11.8 illustrates an example in which the effects of a fixation error are subtler. These mfERGs are from a young woman with a very small central defect in her left visual field. Her acuity was good, and her fixation appeared steady. It was initially thought that her problem was retinal because a few of the paracentral responses (see responses in rectangle) appeared reduced in amplitude. However, an examination of the 3D plot indicated that she was fixating slightly off center; this is easy to see when the 3D plot is compared to the plot from her unaffected right eye.

In sum, if care is not taken in the recording and interpretation of mfERGs, then depressed responses caused by fixation errors can be misinterpreted as a retinal problem.

Ruling Out Functional or Nonorganic Causes

When diagnosing optic nerve disorders, it is often important to rule out functional or non-

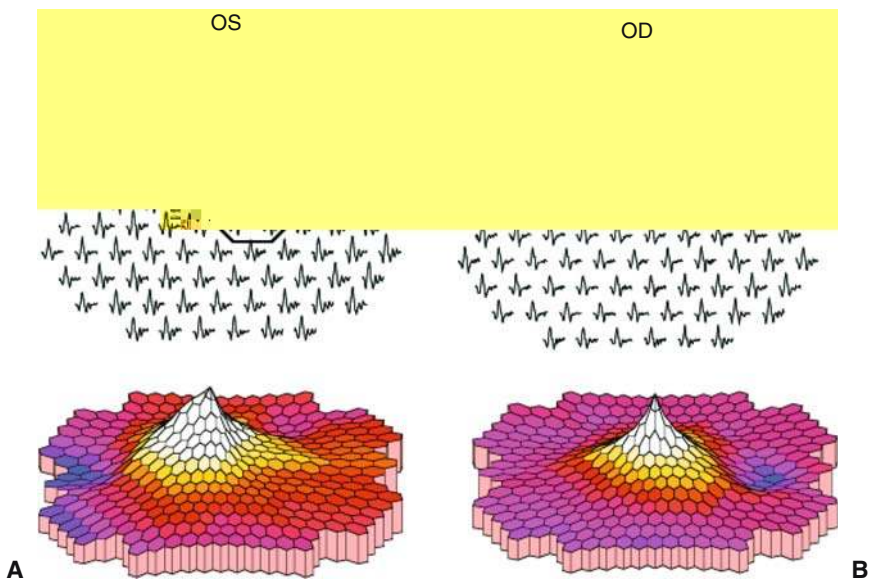

FIGURE 11.8. The problem of eccentric fixation. **(A)** mfERG from the two eyes of a patient. The left eye had a small central defect on the visual field and the right eye had a normal visual field result. The *black circle* indicates an area of apparently decreased mfERG responses. **(B)** 3D plots for the mfERGs in **A**. The 3D plot for the left eye indicates that the patient was fixating slightly off center, which could account for the reduced mfERG amplitudes in that area.

organic causes. The advantage of the mfERG technique over the conventional ERG is that it provides a topographical representation that can be compared to the patient's visual fields. If the mfERG is abnormal in the *same* location as the field defect, then a nonorganic cause can be ruled out. If, on the other hand, the mfERG is normal, then further tests (e.g., the mfVEP) are needed to rule out a nonorganic cause.

Special Techniques for Detecting Ganglion Cell Damage with the mfERG

The effectiveness of the human mfERG for detecting local ganglion cell damage is currently under debate. Although some contradictory findings can be found in the literature, the evidence is relatively clear on the following points. First, there is a component generated at the optic nerve head that appears to reflect local ganglion cell activity. Sutter and Bearse[23] first identified this component in the human mfERG and called it the optic nerve head component (ONHC). Second, a component similar to the ONHC has been identified in the monkey mfERG, and it appears to depend upon ganglion cell activity.[24] Thus far, attempts to detect glaucomatous damage with standard mfERG recordings show relatively poor sensitivity and/or specificity.[8,25–27] However, the relatively small ONHC in humans can be enhanced with specialized paradigms of mfERG stimulation[28,29] and/or methods of analysis.[23] Finally, although clear evidence of local damage has been reported in a few patients, in general the results published to date have been disappointing.[29,30] Thus, it remains unclear whether specialized mfERG recordings can be used to detect early damage in patients with glaucoma. If the results of future studies are more encouraging, then the mfERG technique still needs to be compared to other objective tests of ganglion cell function, such as the pattern ERG (PERG), the photopic negative response (PhNR), and the multifocal VEP. For now, the mfERG cannot be considered a useful clinical tool for studying ganglion cell damage.

The Multifocal Visual Evoked Potential

The VEP has long been used to diagnosis disorders of the optic nerve. For example, delayed VEP responses in patients with optic neuritis/multiple sclerosis (ON/MS) were reported almost 25 years ago.[31,32] While the conventional VEP, elicited by either a pattern-reversal stimulus or bright flash, is still used to help in the diagnosis of ON/MS or to rule out nonorganic (functional) causes, the conventional VEP has its limitations. First, conventional VEPs are dominated by responses from the lower field in most individuals.[33–35] Therefore, in some cases, large defects in the upper field will be missed with the conventional VEP. Second, the conventional pattern reversal VEP is recorded to a display at least 15° in diameter.[36] Thus, local defects can easily be missed. In general, the lack of spatial information can be a problem for the conventional VEP.

The multifocal visual evoked potential (mfVEP), developed by Baseler, Sutter, and colleagues,[37,38] allows the recording of local VEP responses from the visual field by combining conventional VEP recording techniques with multifocal technology. As in the case of the mfERG, each region of the display is an independent stimulus and from a single, continuous EEG signal, the software extracts the VEP responses generated to each of the independent regions. Typically, local VEP responses are generated simultaneously from 60 regions of the central 20° to 25° (radius) of the visual field to create a topographic profile of the visual field.

Recording the mfVEP

For recording the mfVEP, the same electrodes and amplifiers employed for conventional VEP recordings are used. However, the parameters of the stimulus and display and the analysis of the raw records are different. Although new paradigms are being developed,[39] most of the published mfVEP data have been recorded with pattern reversal stimulation and a display similar to the one shown in Figure 11.9. This display, first introduced by Baseler, Sutter, and colleagues,[37,38] contains 60 sectors

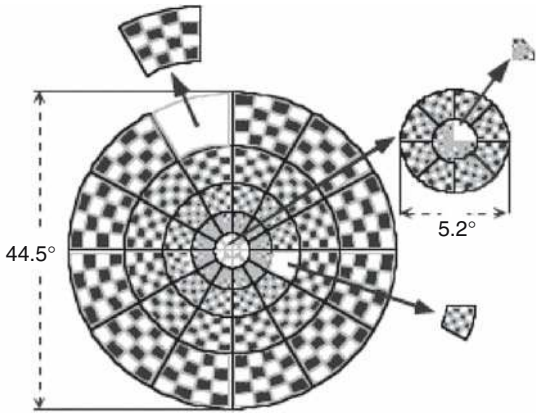

FIGURE 11.9. The multifocal VEP stimulus. This display contains 60 sectors approximately scaled to account for cortical magnification. Each sector contains 16 checks, 8 black and 8 white.

approximately scaled to account for cortical magnification. Each sector contains 16 checks, 8 black and 8 white.

The mfVEP is recorded monocularly with electrodes placed over the occipital region. There is currently no agreement regarding standard placement for the electrodes. However, all mfVEP recordings include at least one midline electrode placement. For example, for our midline channel we use two electrodes. One is placed at the inion plus 4 cm and serves as the "active," and the other, on the inion, serves as the "reference"; a third electrode, the ground, is placed on the forehead. It is not uncommon to record from more than one channel at a time.[40–42] For example, we use three "active" electrodes, one placed 4 cm above the inion and two placed 1 cm above and 4 cm lateral to the inion on each side of the midline.[40,42] Every active electrode is referenced to the inion.

Presentation and Analysis of the mfVEP Responses

Figure 11.10 shows software-derived mean mfVEP responses from 30 control subjects. The black traces are the responses for monocular stimulation of the right eye and the gray traces are the responses from the left eye. As in the case of the mfERG, each of the individual

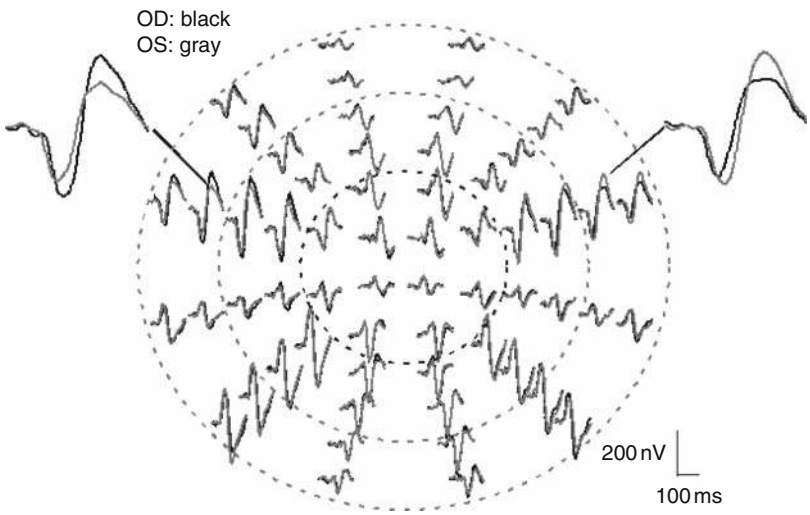

FIGURE 11.10. The software-derived mean mfVEP responses from 30 control subjects. The *black traces* are the responses for monocular stimulation of the right eye (*OD*) and the *gray traces* are the responses from the left eye (*OS*). (Reprinted from Hood,[10] with permission from Elsevier.)

mfVEP waveforms in the array is not, technically speaking, a "response." Rather, each waveform is derived via a correlation between the stimulation and the continuously recorded signal. It is important to note that when the mfVEPs are displayed in an array, as in Figure 11.10, the responses are positioned arbitrarily so they do not overlap. The spatial scale for this array is not linear, which can be seen in a comparison of the iso-degree circles in Figure 11.10 to the display in Figure 11.9. For more details about the mfVEP technique, see recent reviews.[42,43]

Nearly Identical mfVEP Responses from the Two Eyes

There is considerable intersubject variability in the amplitudes and the waveforms of the mfVEP responses. This variability is caused by individual differences in the location and folding of the visual cortex.[21,42] However, the responses of the two eyes from any individual with normal vision are nearly identical, as can be seen in the mean responses of Figure 11.10. These mean responses from the two eyes are nearly identical. The reason for this is that they are generated in the same general cortical regions. The responses from the two eyes do deviate in relatively minor ways. First, there is a small amplitude asymmetry along the horizontal meridian. Second, there is a small interocular latency difference (of 4 or 5 ms) across the midline. These small differences can be seen in the insets in Figure 11.10. The responses from the left eye are smaller, but are slightly faster, than the responses from the right eye in the left visual field, and the reverse is true in the right visual field. (See Hood and Greenstein[42] for a discussion of the reasons for these differences.)

Topographical Representation of the mfVEP

To detect local damage to the ganglion cells/optic nerve requires specialized software, and the current analyses available with commerical equipment are limited. However, this situation is changing rapidly, and the analyses shown here, based upon our software, soon should be generally available in commercial software.To illustrate these analyses, consider the patient whose visual field (probability plot) is shown in Figure 11.11A. This patient had unilateral glaucomatous damage in the left eye; the visual field from his right eye was normal. The defects in the left eye are circled in gray and black. The mfVEP responses obtained from the patient's left eye (red) and right eye (blue) are shown in Figure 11.11B. Iso-degree contours representing the same areas of visual space are shown for both the visual field and the mfVEP responses.

To determine which of the responses from the left eye (red records in Figure 11.11B) are abnormal, mfVEP probability plots analogous to the visual field probability plot in Figure 11.11A were developed. Monocular mfVEP probability plots (left two panels in Figure 11.11C) were obtained by comparing the patient's monocular mfVEPs to the averaged mfVEPs from the left and right eyes of a group of control subjects (see Figure 11.10). For each sector, the amplitude of the patient's mfVEP was determined and compared to the results from a control group.[40,42,44,45] Each square is plotted at the physical center of one of the sectors of the mfVEP display (see Figure 11.9A). A colored square indicates that the mfVEP was statistically significantly different from the control data at either the 5% (desaturated color) or 1% (saturated color) level, and the color indicates whether it was the left (red) or right (blue) eye that was significantly smaller than normal.

Because the visual field (Figure 11.11A) and mfVEP (Figure 11.11C) probability plots are shown on the same linear scale, a direct comparison can be made. To aid in this comparison, the black and gray ellipses from Figure 11.11A were overlaid onto Figure 11.11C. Notice that the mfVEP results confirm the visual field defect within the black ellipse but not the defect within the gray ellipse.

In some patients, especially those with unilateral damage, an interocular comparison of the mfVEP results is a more sensitive indicator of damage than is the monocular comparison to

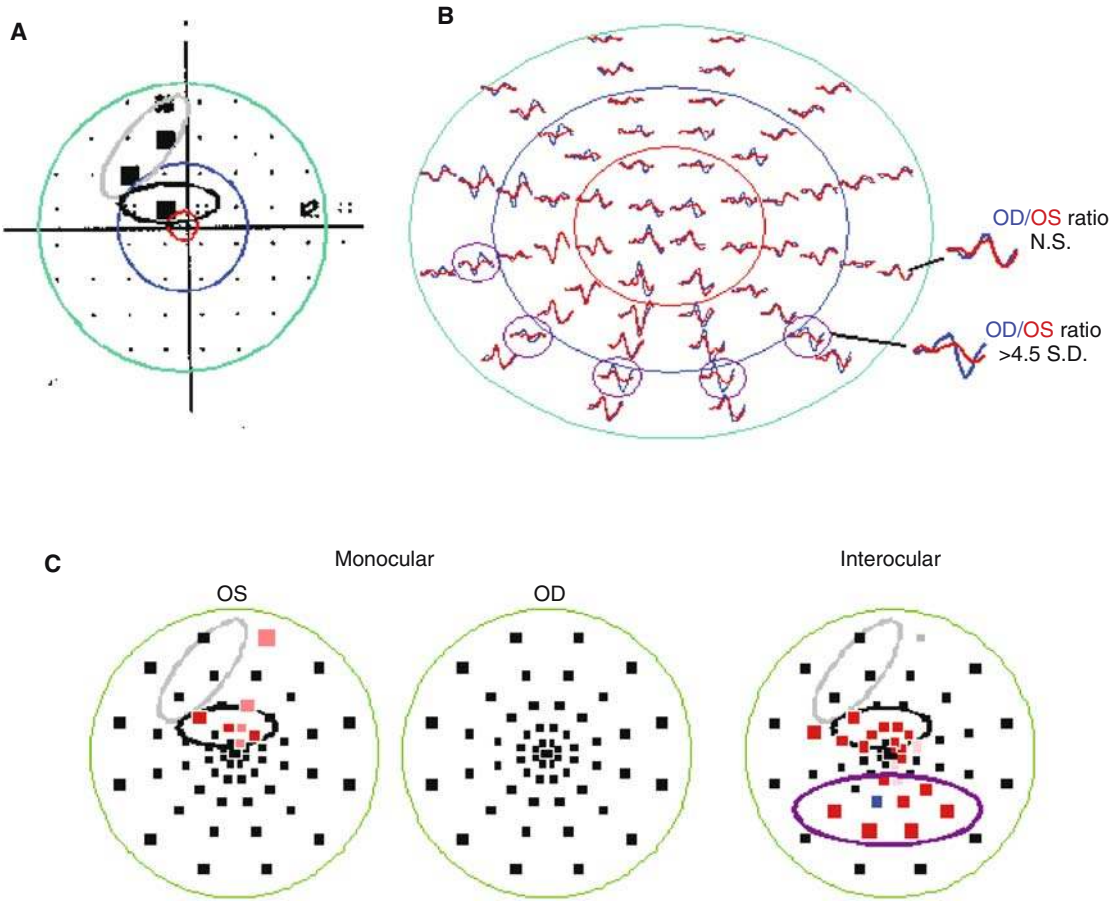

FIGURE 11.11. Results from a patient with glaucoma. **(A)** The 24–2 HVF (probability plot) for the patient's left eye with the defects *circled in gray and black*. **(B)** The mfVEP responses from the patient's left eye (*red*) and right eye (*blue*). *The inset* shows the results of comparing the RMS ratios of two pairs of responses to those from a group of control subjects. *N.S.*, the ratio of amplitudes is not significantly different from normal. Iso-degree contours representing the same areas of visual space are shown for both the visual field and the mfVEP responses. **(C)** Monocular and interocular mfVEP probability plots. Each symbol is in the center of a sector of the mfVEP display. A *black square* indicates that there is no significant difference between the two eyes. The *colored squares* indicate that there is a significant difference at greater than the 5% (desaturated) or 1% (saturated) level. The *color* denotes whether the right (*blue*) or left (*red)* eye had the smaller response. A *gray square* indicates that the responses from both eyes were too small to allow for a comparison. (Modified from Fig. 12 in Hood et al.[11])

the control group.[42,46] To obtain the interocular mfVEP plot in Figure 11.11C (right-hand panel), the ratio of the mfVEP amplitudes of the two eyes is measured for each sector of the display and compared to the ratios from the group of controls.[21,40,42,47,48] The result is coded as in the case of the monocular fields. The defect within the gray ellipse is still not apparent, but an arcuate defect is detected in the lower field that was not present in the visual field. Subsequent tests confirmed that this defect was real. (Hood and Greenstein[42] provide a review of the derivation and use of both monocular and interocular probability plots.)

Measuring Latency as Well as Amplitude

It is now possible to objectively measure the latency of individual mfVEP waves.[49,50] Figure 11.12A shows the visual field probability plot from the left eye of a patient; her right eye had a normal visual field. Figure 11.12B shows the mfVEPs from the right and left eyes. Figure 11.13A shows the amplitude probability plots of her mfVEPs are normal on the monocular plots but that the interocular plot shows a relative loss in amplitude for the left eye. Figure 11.13B shows the results of the latency analysis plotted in an analagous fashion to the amplitude plots. In particular, a colored circle indicates that the mfVEP latency was significantly longer at either the 5% (desaturated color) or 1% (saturated color) level, whereas the color indicates whether it was the left (red) or right (blue) eye that was significantly longer than normal. In this example, the latency of the left eye was, on average, 7.8 ms slower than the right, as compared to the normal control subjects. An individual point is shown that was 15 ms slower on the interocular comparison (i.e., her left eye was delayed relative to her right eye) as well as one that was 34.2 ms slower on the monocular comparison (i.e., relative to the control group).

The Origins of the mfVEP

There are two lines of evidence that the mfVEP is generated largely in V1. First, as originally pointed out by Baseler et al.,[37] the mfVEP waveforms reverse polarity as one crosses the horizontal meridian (see the reversal of the waveforms in Figure 11.10).[42,51] The mfVEP from the upper visual field is reversed in polarity as compared to the lower, whereas the conventional VEP recorded with the same electrodes positions and on the same subjects may show the same polarity for upper and lower field stimulation.[35] Only potentials generated from inside the calcarine fissure should behave this way. Second, a mathematical analysis of the multifocal VEP sources suggests that most of the signal is generated in V1.[52] Third, using an application of principal-component analysis, Zhang and Hood[53] provided evidence that the first principal component of the mfVEP was generated within the calcarine fissure and thus within V1. The clinical implication is that

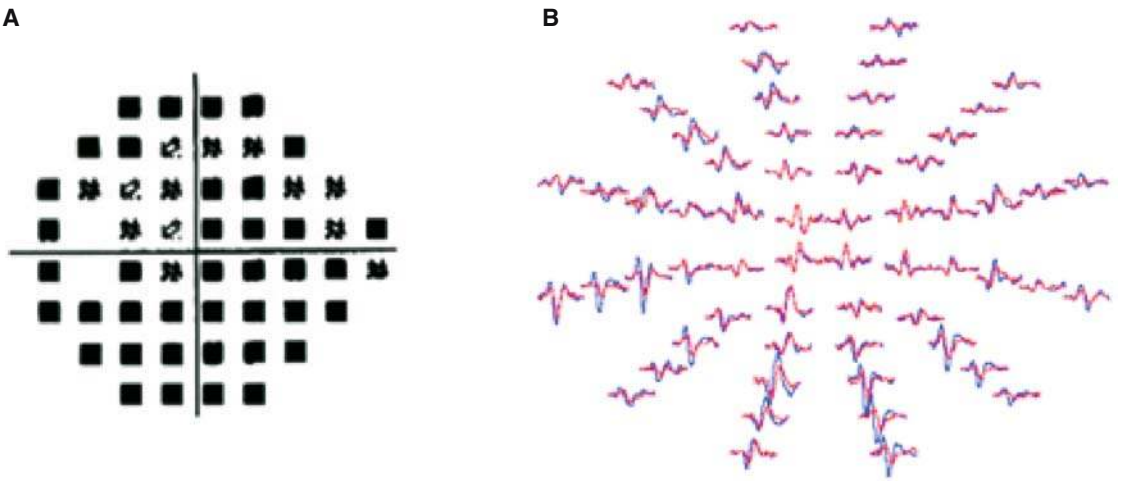

FIGURE 11.12. Results from a patient with vision loss in the left eye. **(A)** The visual field probability plot from the affected left eye of a patient; the right eye was normal. **(B)** The mfVEPs from the right (*blue*) and left (*red*) eyes of the patient.

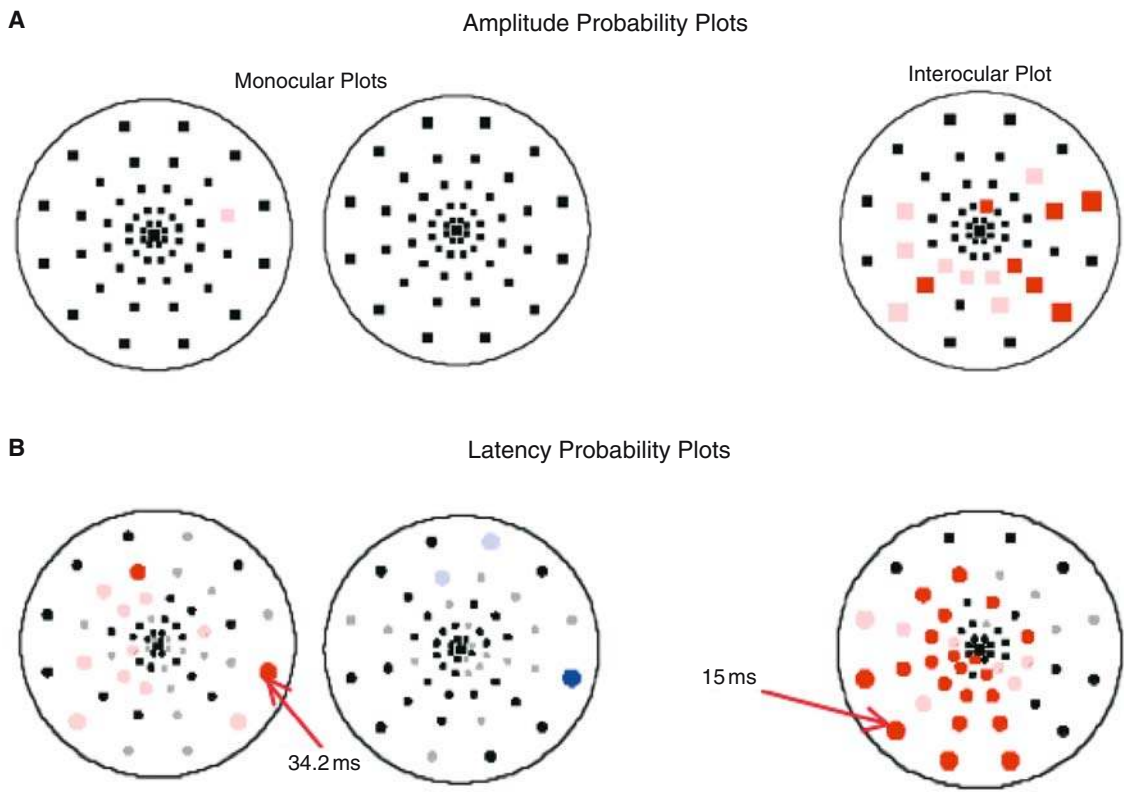

FIGURE 11.13. Monocular and interocular probability plots derived from the VEP results shown in Fig. 11.12. **(A)** Amplitude results. A *colored square* indicates that the mfVEP amplitude was significantly smaller at either the 5% (desaturated color) or 1% (saturated color) level; the *color* indicates whether it was the left (*red*) or right (*blue*) eye that was significantly smaller than normal. **(B)** Latency results. A *colored circle* indicates that the mfVEP latency was significantly longer at either the 5% (desaturated color) or 1% (saturated color) level; the *color* indicates whether it was the left (*red*) or right (*blue*) eye that was significantly longer than normal.

damage beyond V1 does not necessarily produce abnormal mfVEPs.

The mfVEP and the Diagnosis of Optic Nerve Disorders

For a number of years we have recorded mfVEPs from the patients of two neuro-ophthalmologists (Drs. M. Behrens and J. Odel) and two glaucoma experts (Drs. R. Ritch and J. Liebmann). In this section, we summarize the most common uses of the mfVEP in diagnosing optic nerve disorders. Other examples can be found in recent reviews.[42,43]

However, before summarizing the uses of the mfVEP, it is important to understand the effects of local ganglion cell/optic nerve damage on the mfVEP. Hood et al.[46] showed that the signal in the mfVEP response was linearly related to the loss in visual field sensitivity. To take a simple example, this means that a loss of 10 dB in visual field sensitivity will reduce the amplitude of the signal in the mfVEP response by a factor of 10; this will result in an mfVEP response indistinguishable from noise. Therefore, relatively small visual field sensitivity losses (6 dB or so) caused by optic nerve damage produce profound losses in mfVEP amplitude.

The Diagnosis and Follow-Up of Optic Neuritis/Multiple Sclerosis

During the acute phase of ON/MS, mfVEP amplitudes are depressed in all regions where the visual field sensitivity is decreased.[54] Typically, optic neuritis shows partial or complete recovery within 3 months and so does the mfVEP. In fact, those patients with normal visual fields after recovery have normal or near-normal mfVEP amplitudes, although the latency in some regions will be markedly delayed.[54,55] These regions with the delayed mfVEP presumably correspond to the portions of the optic nerve that were demyelinated. The mfVEP records in Figure 11.14B show the range of findings that can be observed in a patient who had an attack of optic neuritis in the left eye.[54,55] In this case, the visual field probability plot (Figure 11.14A) shows a paracentral defect and the amplitude of the mfVEP is depressed in this region (ellipse in Figure 11.14B). However, the mfVEP (Figure 11.14B) shows that outside of this region there are areas with delayed mfVEP responses (asterisks) and regions with reasonably normal mfVEP responses (plus signs). In fact, regions with delays can border regions that have responses with normal amplitude and latency. Thus, the mfVEP is able to detect local demyelinizaton.[54]

Therefore, for diagnosing patients with ON/MS, the mfVEP is superior to SAP and the conventional VEP. We have seen a number of cases of ON/MS in which the mfVEP was abnormal but the conventional VEP was normal. In these patients, whether the conventional VEP is normal depends upon the relative contributions of the normal and abnormal regions of the visual field. The conventional VEP is most likely to miss local delays if the delays involve very small areas or occur in the upper field, which typically contributes less to the overall VEP signal than does the lower field.[35] Figure 11.15 shows the SAP probability plot (panel A) and mfVEP responses (panel B) of a 45-year-old man who complained of blurred

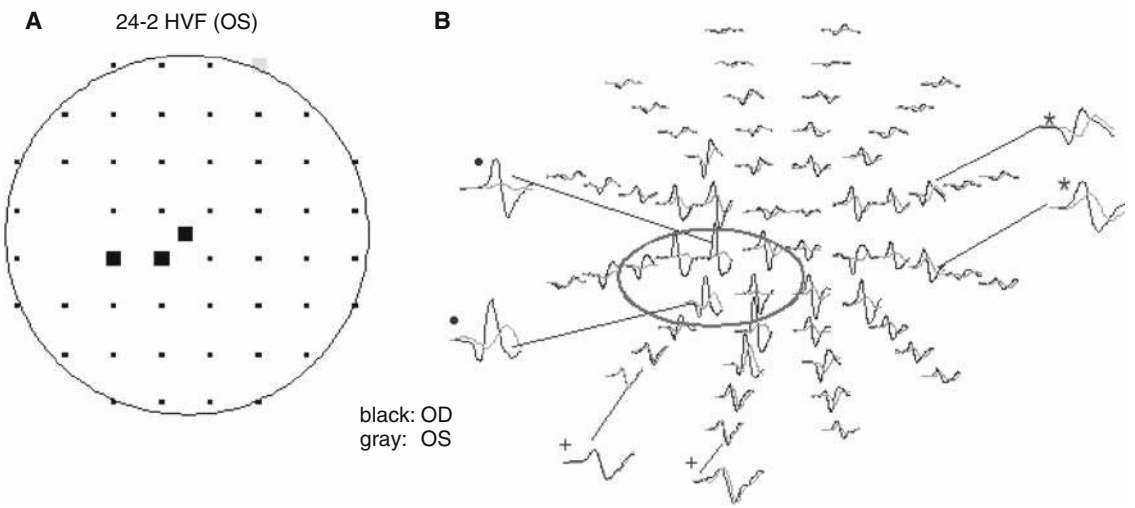

FIGURE 11.14. Results from a patient with optic neuritis in the left eye. **(A)** The visual field probability plot from the left eye shows shows a paracentral defect. **(B)** The mfVEPs from the left eye show depressed amplitudes in the area that was affected on the visual field (*ellipse*). However, outside this region there are areas with delayed mfVEP responses (*asterisks*) as well as regions with reasonably normal mfVEP responses (*plus signs*). (Reprinted from Hood,[10] with permission from Elsevier.)

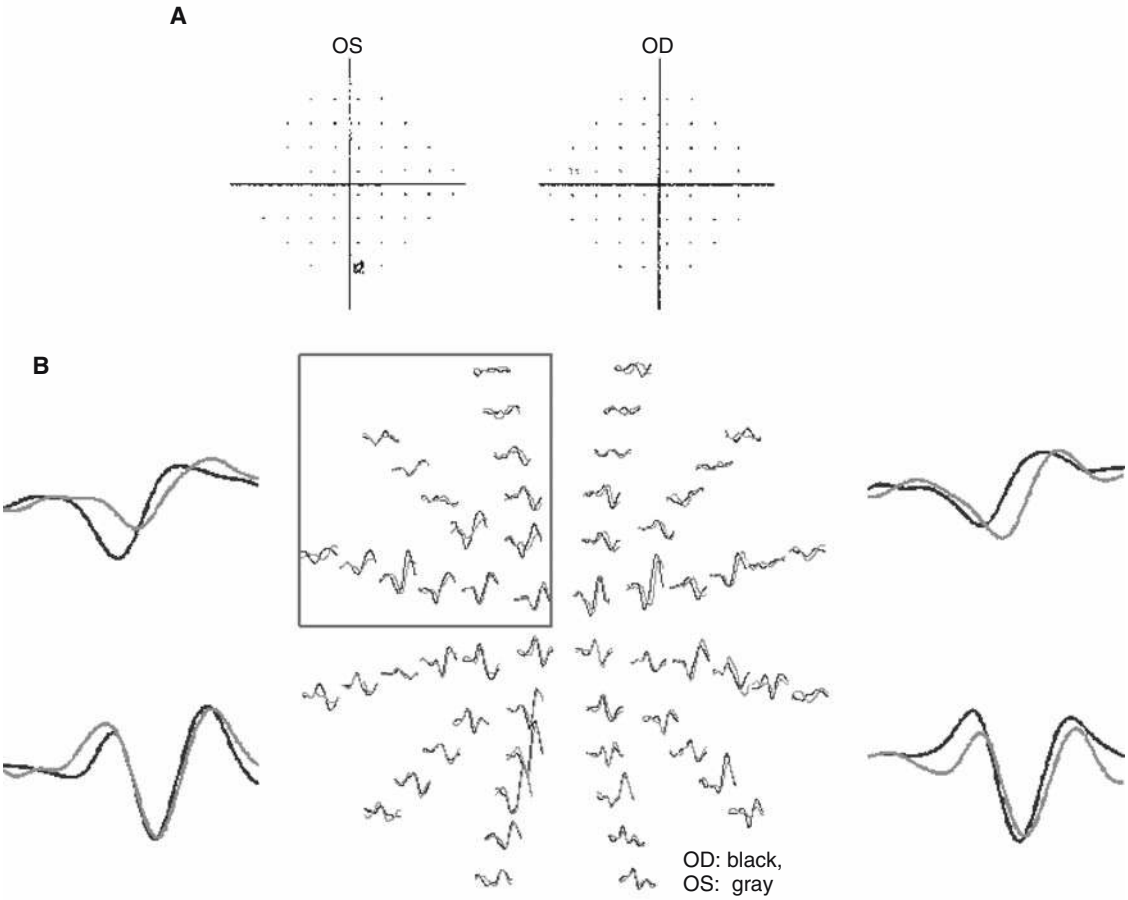

FIGURE 11.15. Results from a patient with blurred vision in the superior field of the left eye. **(A)** The visual fields for the left and right eyes were essentially normal. **(B)** mfVEP response arrays for the left (*gray*) and right (*black*) eyes. The *insets* show the mfVEPs summed within each quadrant, indicating delayed mfVEPs in the upper field for stimulation of the left eye. (Modified from Fig. 14 in Hood et al.[11])

vision in the superior field of his left eye. The diagnosis of MS was confirmed from magnetic resonance imaging (MRI) studies, which showed lesions in the left optic nerve. His conventional pattern VEP, as well as his SAP fields (panel A), were normal. The insets in panel B show the mfVEPs summed within each quadrant. The mfVEPs are clearly delayed in the upper field for the left eye. This change was missed on the conventional VEP, presumably because the upper field contributed relatively little to the conventional VEP.

Although the diagnosis of ON can usually be made based upon the patient's history and visual fields, a small percentage of the patients with ON can present with swollen discs but without pain. In these cases, it is important to distinguish between ON, ischemic optic neuropathy (ION), or a compressive lesion. We have found the mfVEP useful in these cases.[43]

Finally, the mfVEP is particularly useful for following patients with ON/MS, especially in cases in which the visual field is normal. We have recently documented recovery of local mfVEP latencies in some patients whose visual field thresholds are normal and stable.[56]

Ruling Out Functional or Nonorganic Causes

The conventional VEP has been used to rule out functional or nonorganic causes for visual defects. Because multiple, local responses are obtained, the mfVEP is more effective than the conventional VEP for this purpose. For example, a local defect can be identified on the mfVEP and can be missed on the conventional VEP if the defect involves a small part of the total field stimulated. In these cases, the (incorrect) diagnosis of a functional cause can be avoided. Figure 11.16 provides an example of a patient whose complaint of a localized visual loss was thought to be nonorganic in nature. His fields were unreliable, and he was under emotional stress at home and work. However, his mfVEP confirmed a local deficit in the same general region as his complaint. The local change in the mfVEP can be seen in the records of panel A and the interocular probability plot of panel B. The mfVEPs and the corresponding SAP points illustrate the local loss. Subsequent tests revealed a diagnosis of Leber's optic atrophy. In patients such as this one with localized deficits, the conventional VEP is often normal.

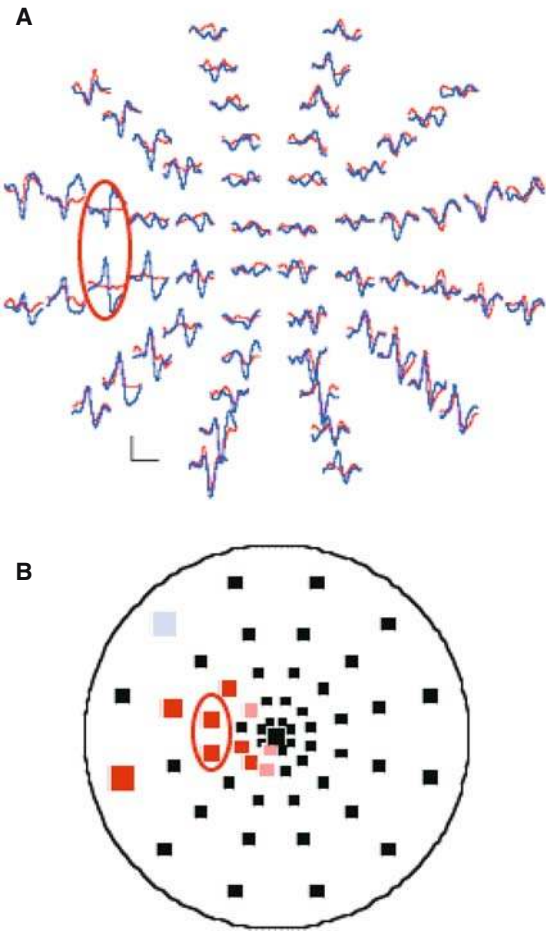

FIGURE 11.16. Results from a patient with a localized vision loss. **(A)** The mfVEP plots for the left (*red*) and right (*blue*) eyes. **(B)** The mfVEP interocular probability plot reveals local losses (*red circle*).

Conversely, when faced with normal mfVEP responses in regions of the field where the visual field shows a profound defect,[57] the ophthalmologist will be comfortable making a diagnosis of a nonorganic cause. In fact, the mfVEP, with its topographical measures, provides more information and a greater degree of certainty than does the conventional VEP.

Finally, it is also possible to assess the patient with "functional overlay." That is, it is not uncommon to have a patient with clear indications of organic disease, but whose visual fields are too bad to be explained by what appears to be the organic cause. A careful quantitative comparison of the mfVEP amplitudes can help to parcel out the nonorganic contributions from the organic ones.

Questionable Fields or Fields That Need Confirmation

A related category of patients are those whose visual fields are questionable to the ophthalmologist even though the reliability indices are within the normal ranges. That is, the visual fields do not appear to reflect the other clinical findings. For example, some patients produce visual fields on SAP that are reproducible and of good quality (e.g., false positives, false negatives, and fixation errors are low), but which are nonetheless not a veridical indicator of what the patient actually sees. In such cases, the ophthalmologist often has insufficient or contradictory evidence, making it difficult to diagnose the cause of a defect seen on the SAP. Figure 11.17 shows an example of a 74-year-old woman with abnormal visual fields. These fields

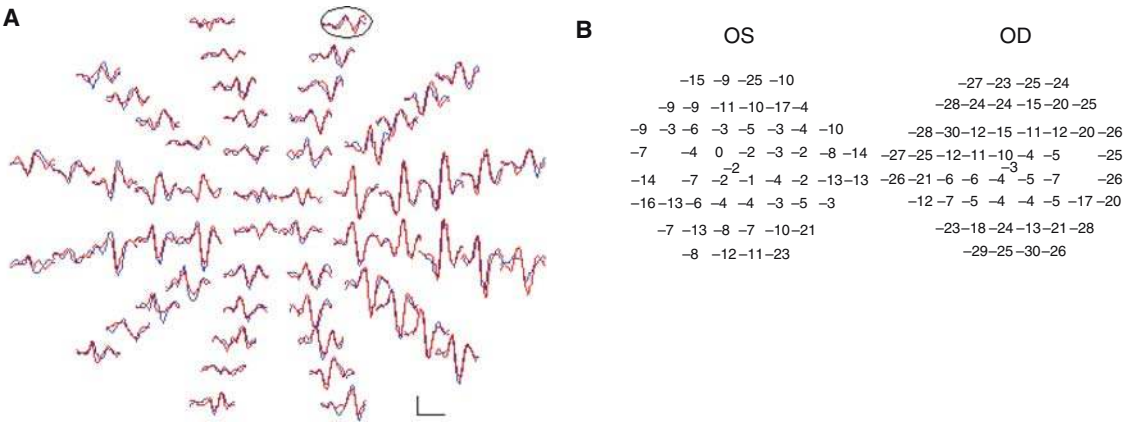

FIGURE 11.17. Results from a patient with abnormal visual fields. **(A)** mfVEP plots for the left (*red*) and right (*blue*) eyes. **(B)** The Humphrey 24–2 total deviation plots for this patient reveal large losses in sensitivity that do not agree with the mfVEP findings shown in **A**.

would not be classified as unreliable based upon standard statistics. Notice in Figure 11.17B (24–2 Humphrey total deviation plots) that both eyes had regions of sensitivity loss that exceeded 15 dB. Her ophthalmologist questioned the fields because her cup-to-disc ratios [0.6 (OD) and 0.5 (OS)] were relatively good whereas her fields were very poor. The mfVEPs were obtained, and they were inconsistent with her visual fields. The mfVEP responses from both eyes (Figure 11.17A) were quite robust, which did not agree with the large visual field sensitivity losses. Remember that optic nerve damage produces profound decreases in the mfVEP (see foregoing discussion; also Hood et al.[46]). Other examples of the use of the mfVEP to confirm qustionable fields can be found in published reviews.[42]

Unreliable Visual Field Test Takers

Many patients cannot or will not reliably perform SAP. For most of these patients, the mfVEP provides an alternative.

Detecting Glaucomatous Damage

Most of the work with the mfVEP has focused on glaucoma. A detailed description of this work is beyond the scope of this chapter. Fortunately, reviews on the use of the mfVEP in detecting and following glaucoma are available.[42,58] Our own view is that the mfVEP can be very useful to the glaucoma expert. It can be used to test unreliable field takers and patients with questionable fields or fields that need confirmation. However, we do not believe that in its current form it will replace SAP. Although there are conditions under which the mfVEP can detect damage missed on SAP,[42,48,59,60] there are conditions under which the reverse is true.[42,60]

The Problem of Fixation Errors

Unsteady fixation can cause diminished responses in the center of the field.[42,60] Inaccurate or unsteady fixation will affect the mfVEP results.[42,60] Monitoring the eye will assure that fixation is steady, but it will not guarantee that the fixation is accurate. Some patients with central visual problems can have eccentric fixation. Figure 11.18 shows the effects of a 3° fixation error. A control subject was instructed to maintain a steady fixation that was down and to the left by 3° for the right eye while the left eye was tested with central fixation. Compared to the control condition (Figure 11.18A,B), the

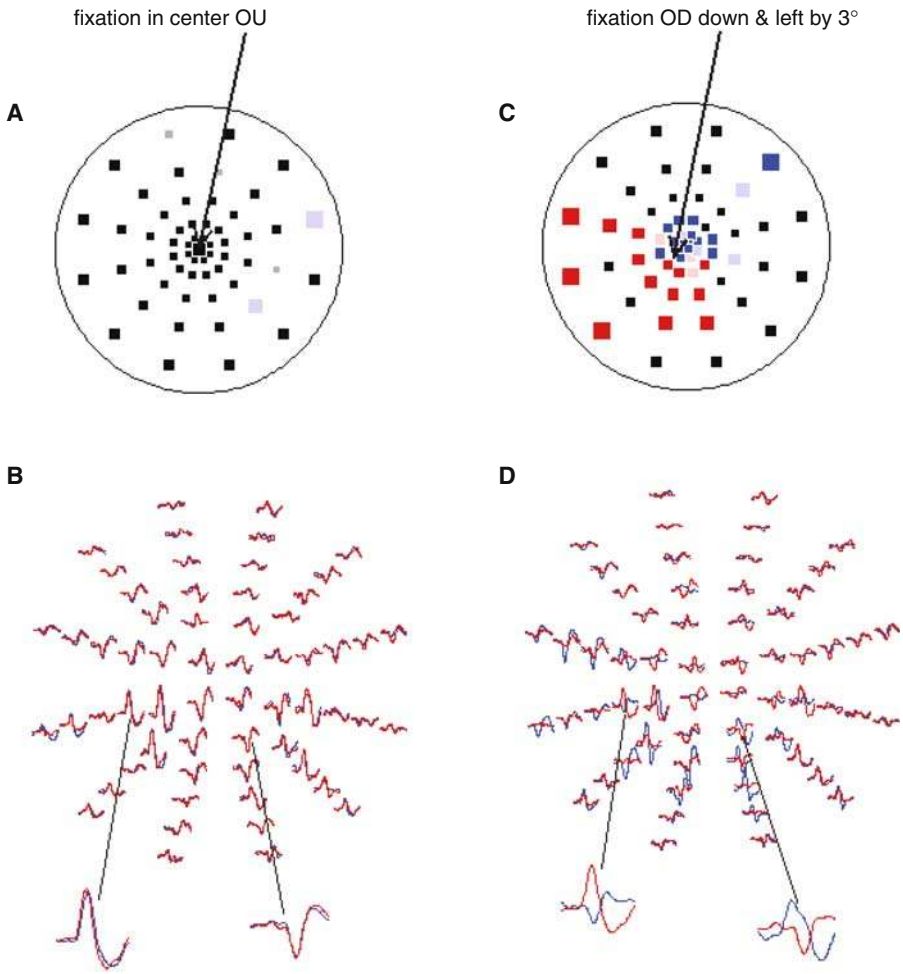

FIGURE 11.18. The consequences of eccentric fixation. Eccentric fixation can give the appearance of an abnormality in an otherwise normal eye. **(A)** Interocular mfVEP probability plot for a control subject fixating at the center of the stimulus when testing both eyes. **(B)** The 60 mfVEP responses corresponding to the probability plot in **A**. Responses in the *inset* are of the same polarity and appear normal. **(C)** Interocular mfVEP probability plot for the same subject instructed to fixate down and to the left by 3° when testing OD and fixating in the center when testing OS. **(D)** The 60 mfVEP responses corresponding to the probability plot in **C**. Responses in the *inset* show clear polarity reversals and amplitude differences between the two eyes. (Reprinted from Hood et al.,[43] with permission from Lippincott Williams & Wilkins.)

eccentric fixation condition (Figure 11.18C,D) showed apparent defects in both eyes on the interocular probability plot. It is relatively easy to tell that these "defects" are caused by eccentric fixation. The probability plot shows a telltale sign. In particular, there are smaller responses in diagonally opposite parts of the field. Confirmation that these symmetrical defects are caused by an eccentric fixation can be obtained by examining the responses from near the midline. Notice that some of these responses (see inset in Figure 11.18D) show a polarity reversal between the two eyes. Thus, it is important to monitor eye position to avoid

false positives from unsteady fixation. In addition, the mfVEP plot and responses (see Figure 11.18) should be examined to avoid false positives resulting from eccentric fixation.

Poor mfVEP Test Takers

Just as there are patients who are unreliable SAP takers, there are also patients who have great difficulty being tested on the mfVEP. In a few cases, these can be the same individuals. Patients who refuse to cooperate or who go to sleep may be difficult to test on either SAP or the mfVEP. In our experience, however, the overwhelming majority of the patients who are poor SAP takers are able to perform the mfVEP test. On the other hand, there are a small percentage of patients who are good SAP takers but who do not produce usable mfVEP recordings. In these cases, the responses are difficult to discern because of a high noise level secondary to either a large alpha-wave contribution or poor signal-to-noise ratios in general.

When Is the Multifocal Electroretinogram and/or Multifocal Visual Evoked Potential Test Needed?

The mfERG and mfVEP are not necessarily the best electrophysiological tests for every patient. In deciding whether an mfERG or mfVEP is the appropriate test, the following points should be kept in mind:

1. If there is no advantage to performing a multifocal test over a full-field test, then the standard full-field ERG or conventional wide-field VEP should be performed first. In general, the multifocal tests take more time to administer, require more technical expertise to perform and analyze, and are less readily available than the conventional ERG or VEPs.[61] For example, if the problem is panretinal (a large area of the visual field is abnormal), and the ophthalmologist wants to determine if there is retinal involvement, then a standard full-field ERG[62] is the test of choice.

2. The mfERG and mfVEP are not useful for problems in the far periphery. In general, these tests assess performance on the central 20° to 30° from fixation (see Figures 11.1A and 11.9).[61]

3. These tests do not assess rod system function. These techniques test the cone system: the cone receptors and cone bipolars are assessed when recording the mfERG, and the cone pathways up to V1 are assessed when recording the mfVEP. This is another reason for using the ISCEV standard full-field ERG, which tests rod and cone system function, if panretinal damage is expected.[61]

4. These tests are not appropriate if the patient cannot maintain fixation or has nystagmus. Under these conditions, the mfERG and mfVEP can be a challenge to interpret, whereas the standard ERG and VEP are more immune to eye movements and fixation problems.[61]

5. If you are going to perform a multifocal test, always attempt to obtain a reliable visual field using SAP. We repeat that the power of the multifocal technique is that it provides topographical information. This advantage is poorly used without a comparison of the deficits seen on the multifocal test with those seen on SAP.[61]

To conclude, when faced with localized damage of the visual fields in patients with steady fixation, the mfERG and mfVEP are powerful tools for diagnosing and studying disorders of the optic nerve.

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